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Editorial

Emotional Stress and the Etiology of Coronary Artery Disease

ALTHOUGH the etiology of coronary atherosclerosis remains unknown, two major theories exist as to its causation. One ascribes the origin of the pathologic process to an abnormal lipid level in the blood, either total lipid or some fraction of lipoprotein. The other considers the cholesterol deposit to be secondary to repeated thromboses ineffectively neutralized by normal fibrinolytic processes.[1] The two mechanisms may be related in some way to abnormalities of fat metabolism, since both hypercholesterolemia and thrombotic episodes appear to be more common in populations with a high fat intake. Nevertheless, scientific proof of a causal relationship between fats in the diet, the blood lipids, and coronary artery disease is still lacking. Even in countries where fat consumption is high most of the population does not suffer from clinical coronary disease, and of those individuals who do, a large segment exhibits normal blood lipid findings. Considerable overlapping exists therefore between the lipoprotein patterns observed in patients afflicted with myocardial infarction and those encountered among apparently healthy controls. Indeed, studies of patients with angina pectoris have been reported as showing no significant differences by such measurement when comparison was made with findings in persons without clinical disease.[2] Thus, while one cannot deny that deranged lipid metabolism may be one of multiple predisposing causes of coronary atherosclerosis, an individual susceptibility appears to exist which is not well understood and which may be determined by such factors as heredity, constitution, coagulation mechanisms, hormones, physical exercise, emotional stress, and other characteristics of the mode of life or environment, acting singly or in combination.

The Factor of Mental and Emotional Stress: In recent years, many authorities have challenged the scientific basis for the clinician's impression and layman's conviction that mental stress or emotional disturbances predispose one to coronary artery disease. It has been stated that attacks that are attributed to "hard work, laudable ambition and devotion to duty" may in reality be the result of "physical indolence and gluttony."[3] There is no doubt that emotional tension may result in compulsive eating, drinking, and smoking in many individuals as compensation for anxiety. Moreover, it does frequently contribute to the failure to achieve daily exercise "by promoting fatigue and by forcing a man to make so many commitments that no time is found for exercise, such as walking."[4] While recognizing the probable significance of such indirect effects of emotional stress, it is no longer necessary or useful to consider its influence on cardiovascular function and structure in terms of vague assump-

tions. In such illnesses as hypertension, asthma, colitis, and peptic ulcer, there are fairly well understood neural pathways and circuits involving the autonomic nervous system through which emotions can affect smooth muscle, glandular secretions, or both.

In like manner sympathetic adrenergic effects on vascular tissue metabolism as a result of stress appear to contribute to atherogenesis to a much greater extent than is being generally appreciated.[5] It is well known that stress reactions are commonly associated with fluctuations of epinephrine, hypothalamic overactivity, and cortical and autonomic imbalance. What is not generally known, however, is that the deposition of cholesterol in the intima is accelerated and intensified by epinephrine and that catecholamine-phospholipid compounds seem to possess a particular affinity toward arterial tissue.[6,7] The arterial walls contain relatively large quantities of potentially injurious catecholamines (epinephrine from the adrenal medulla and arterenol from the sympathetic nerve terminals), the tissue necrosing properties of which have long been recognized. These hormones, by primarily injuring the intima, may prepare the soil for subsequent lipid depositions. Catecholamines diminish myocardial efficiency and by wasting oxygen in a disproportionate fashion are capable of inducing severe potentially necrotizing myocardial hypoxia.[8]

The struggle for material success in a conformist competitive society with its many frustrations and anxieties may thus exert detrimental effects on the cardiovascular system through adrenergic and other stress responses. Indeed Weiss and associates[9] as well as others have reported that gradually mounting tension of emotional origin, months or years in duration, occurred prior to the onset of coronary occlusion in a large segment of the patients coming under investigation. Such observations appear to correlate with the finding of abnormally high concentrations of epinephrine in the myocardium of persons who had died after recent myocardial infarction.[10]

Stress and the Endocrine System: Since the relationship between nervous stimuli and endocrine gland function is close, inability to compensate adequately for changes in environmental responsibilities also can be readily transmitted to the endocrine system by way of the cerebral cortex and hypothalamus. It is known that long continued stress can produce a variety of adaptive responses such as have been elaborated upon especially by Selye.[11] Yet it has been questioned whether the stresses of a magnitude compatible with a "normal" life can influence the deposition of cholesterol material in coronary vessel walls. Certainly acute stress can lead to profound disturbances in endocrine function. For example, acute anxiety or shock may precipitate hypoglycemia and gastrointestinal erosions by disturbing normal pituitary-adrenocortical balance, or thyrotoxicosis by altering normal pituitary-thyroid balance, or amenorrhea and impotence by influencing normal pituitary-gonadal relationship. Although no marked consistent abnormality of endocrine gland function has yet been found in patients with clinical coronary artery disease, comparatively minor disturbances could be easily overlooked with available methods.

The evidence strongly suggests that the maintenance of normal cholesterol metabolism and of the coagulation-fibrinolysis system could be disturbed by an alteration of the physiological endocrine balance. Rosenman and Friedman[12] have reported on tests performed on tax accountants who had worked under pressure to make deadlines. They found that the amount of cholesterol went up markedly when the accountants were under stress while the tendency of the blood to clot increased. Cathey[13] has similarly observed that serum cholesterol levels are related to the life situation and to the individual's reaction to those situations. Thus, in patients with a history of myocardial infarction, periods of high serum cholesterol were almost invariably related to episodes of emotional stress. Similar findings have been noted by others in healthy students during examination week.[14] While the exact mechanisms underlying such changes are not yet clear, elevation in plasma cholesterol is seen with decreasing estrogenic, thyroid and adrenocortical activity and with increase in androgens. Adrenocorticotrophin (ACTH) and cortisone tend to shorten clotting

time and to inhibit fibrinolytic activity while epinephrine increases the clotting tendency and favors fibrinolysis.

Stress and Coronary Atherosclerosis: From all the evidence it would appear that emotional stress acting through the cerebral cortex and hypothalamus via neurohormonal and hormonal mechanisms may be responsible for (1) an increase in the lipid receptiveness of the vascular walls, (2) an elevation of blood cholesterol and, (3) an acceleration of blood clotting time. Variations in the receptiveness of the vascular walls to cholesterol deposition and in blood clotting time could explain the lack of a close correlation between blood lipid levels and clinical coronary disease as well as the weak predictive significance of cholesterol determinations and lipoprotein patterns of the blood.

In a person whose coronary circulation is already impaired, one can trace the sequence from emotional upset to acute coronary occlusion and/or myocardial infarction through known mechanisms, i.e., acceleration of blood clotting time, increased heart rate and cardiac output, elevation of blood pressure and necrotizing myocardial hypoxia (catecholamines). The major question, however, is not whether emotional factors may precipitate an acute coronary episode but whether or not such factors may be causally related to the genesis and progression of coronary atherosclerosis itself. The evidence cited lends support to the view that such a relationship does exist while the findings in young coronary groups add further confirmation to this concept. Thus, Gertler and White[15] as well as Yater and co-workers[16] have clearly shown a considerable difference in the type of civil positions held by young coronary patients as compared with controls. The young coronary patient, they found, almost always had occupied a position demanding responsibility and frequently associated with emotional stress. Our own studies in a group of 100 young coronary patients between the ages of 25 and 40 years have shown that emotional strain associated with job responsibility was the most prevalent factor, followed by diet and heredity.[17] Thus, it was found that 91 per cent of the coronary patients as compared with 20 per cent of the controls had been under unusual occupational stress for varying periods preceding the attack. Similarly, it is of interest that the same studies of the Bantus and other groups which have gained recognition for the role of diet,[18] have shown that if job responsibility were used as an index, as good a correlation could be found between it and the increased incidence of coronary artery disease as was found with the fat intake.

Personality and Behavior Patterns in Coronary Patients: The coronary patient has been characterized as possessing certain personality factors and behavior patterns.[19] It is claimed that he is an unremitting worker who adheres to one occupation for many years, working long hours without vacations under considerable "stress and strain." He is alleged to have little interest in sports, few hobbies, but marked interest in philosophy and intellectual occupations. It is further claimed that he possesses a low awareness of body symptoms. According to this view, therefore, the candidate for coronary artery disease usually is an aggressive, ambitious individual with an intense physical and emotional drive, unable to delegate authority or responsibility with ease, possessing no hobbies and concentrating all of his thoughts and energy in the narrow groove of his career. Although Miles and associates[20] were unable to confirm the existence of a "coronary personality" our findings have convinced us that certain personality traits and behavior patterns are fairly characteristic of the young candidate for coronary disease. Almost invariably he was found to be a hard-driving, goal-directed individual who lived beyond his normal capacity and tempo and who minimized his symptoms and neglected prudent rules of health. Contrary to the findings of others, however, many of our young coronary patients were keenly interested in sports and some had many hobbies. Indeed, often they could be distinguished from the controls by the fact that in participating in extracurricular activities, civic affairs, and hobbies, they frequently took on far more than good judgment would appear to dictate.

Statistical and Geographic Observations on Stress: Numerous arguments have been advanced against the acceptance of emotional stress as a significant factor in the genesis of coro-

nary heart disease. It is reported that in Japan hypertension is prevalent, and so is suicide, but coronary disease is rare.[21] It is also alleged that in manic depressive psychosis both in its agitated and depressed phases, severe turmoil exists and yet life expectancy is not significantly altered.[22] Buck[23] has shown, however, that patients, with functional psychoses have a raised death rate from cardiovascular disease. Arnott[3] commenting on the alleged high incidence of coronary disease in the professions with most responsibility to bear, has stated: "The life of a physician in Birmingham is surely much less stressful than that of a peasant in the Yangtse valley, with the ever present menace of flood, famine, pestilence and war." It is repeatedly claimed that periods of presumptive stress, as during the occupation of Norway and the Netherlands, have not been remarkable for any general increase in cardiac death rates.[24]

Such observations are most difficult to interpret because the validity of the statistics from which they are derived is open to question and because emotional stress itself cannot be quantitated by present methods. It would seem, however, that when whole populations are simultaneously subjected to stressful patterns of living, emotional strain becomes the "norm" and physiologic adjustments occur more readily than when one individual is waging a "cold war with his cultural environment."[25] Certainly, support for the etiologic role of emotional factors is provided by Morris' observations[26] of a significantly higher mortality from coronary disease among general practitioners than among specialists in other branches of the profession, and from the finding that, in Germany after the war, when political tensions were severe, the deaths among representatives in government during the first session were significantly above expectations.[27]

The high incidence of coronary disease in the United States might, at first, appear to offer a contradiction to the importance of emotional stress in the etiologic picture of this disease. If we are to accept the data of statisticians, ours is a civilization that enjoys more leisure than any in history. In theory, at least, there can be no disagreement with this finding. In reality, however, this era of less work and more play is a tormenting illusion. It has been pointed out that the majority of us work harder—at something—than we have ever done before.[27] One in every 20 workers, according to the U. S. Census Bureau, is holding down two jobs and some 100,000 are managing three. Store owners work more than 50 hours per week and physicians commonly work more. Despite mechanization, farmers are still engaged in their occupation at least 50 hours per week while top corporation executives spend 60 hours a week at their jobs including the work they take home. Nearly a third of married women are employed outside their home thus adding a job to one they already have, while men whose wives work also take on the extra job of helping to run the house. It is not until the average American arrives home at the end of the day, however, that the pressures of our society really start to close in on him.[28] Far from being free from the demands of work or duty, much of his leisure time is regimented by participation in adult classes at night school, bowling, volunteer work, dancing lessons, bridge, community drives for funds, club meetings, and the like. Such obligatory use of leisure is not satisfying and may represent a poor antidote for the emotional stresses of daily business competition.

Clinical Implications: Some authorities have warned of the dangers of assuming that emotional stress is an important agent in the etiology of coronary disease. They fear lest this view, by creating the belief that emotional stress is always bad, may strip human life of its higher values and incentives and lead to unimaginative boredom. With proper perspective, however, mental and spiritual creativeness need not be sacrificed for the enjoyment of a full life. Perhaps Sir Thomas Lewis' description of a prudent way of life would not appeal to some of us, but its practice would no doubt be a forward step in the control of our nation's number one public health problem. "Very prudent people," said Lewis,[29] "live quietly and moderately; they have their simple daily routine of work and pastime, enlivened by occasional excursions and entertainments, social gatherings and visits to and from their friends. They are temperate in their eating, taking no more than will maintain them in robust health, arranging their diet to consist chiefly of plain good food, relieved occa-

sionally of its monotony by a more elaborate, but not heavy meal. They are regular in their habits of work and exercise, and in their mealtimes. They are strictly temperate in their drinking. They control their emotions and their passions. They avoid all forms of excess. They use tobacco little if at all. They welcome the freshness of abundant air and open spaces, delighting in the feelings of invigoration that accompany active exercise; they love the warmth of sunlight playing on their skins and the sleepiness of healthy fatigue. These are habits that few people in industrial countries now adopt, that fewer still maintain. The cares and distractions of an increasingly complex life, indoor or sedentary occupation, advancing years and decreasing energy interfere less or more, and the prudent rules are neglected; neglect is the easier because the penalties, owing to the body's great power of resistance to disease, are uncertain in their incidence and often long deferred."

Healthy habits would become more prevalent if the consequences of their neglect were more immediate and variable. Indeed, healthy habits, an optimistic philosophy, and the sound use of the abundant leisure which has made us the envy of the world, might well neutralize or retard the atherogenic mechanisms which are both initiated and accelerated by the "stress and strain" of our daily struggle for existence.

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Symposium on Mitral Regurgitation (Part II)*

Hemodynamics of Mitral Insufficiency†

Observations from Clinical and Experimental Surgery

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THE PROBLEMS of surgical treatment of cardiovascular disease are far from limited to the invention of technics with which to effect anatomic or mechanical changes in the damaged structures. The early years of cardiac surgery have seen many ingenious surgical procedures come and go because, among other reasons, they were not planned with the ultimate fate of the tissues affected in mind, or because they were applied in instances where fundamental physiologic alterations were not well understood. Such has been the case in mitral insufficiency. The early efforts, aimed at restoration of valvular substance,[1–20] ignored the basic anatomic and histopathologic complex and neglected the possible consequences to trauma inflicted upon intracardiac tissues. In the numerous clinical trials of some of these procedures little or no effort was made to elucidate their physiologic rationale or sequellae.

The concept of reduction of annular size as a means of attaining reduction in size of the regurgitant orifice, restoring valvular leaflet mobility, and accomplishing permanent stabilization of the annulus has been the subject of the author's interest since 1952 and has been intensely investigated since that time.[21] It has been documented that this approach is mechanically and anatomically sound.[22–26] In the course of these studies particular attention has been focused upon the physiologic problems of mitral regurgitation.[26] It is these aspects which are discussed in this paper.

The voluminous literature on this subject[22,27–62] shows a progressively better understanding of the hemodynamics of mitral insufficiency beginning with the classic work of Wiggers and Feil[30] which established the fundamental mechanisms involved in this valvular derangement.

Inferences drawn from the existing information could be applied to the prediction of the physiologic sequellae following correction of mitral regurgitation in patients, within the limits which qualify the data. These are the lack of true controls in clinical material on one hand and, on the other, the influence of experimental conditions in studies on animals which are, to begin with, free of the inflammatory corollary and of the chronicity of rheumatic heart disease in man. Nevertheless, the accumulation of observations[26] made possible by an effective surgical corrective method shows the findings to be of a character which, although unprecedented, could have been predicted in most instances. There are some cases, however,

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which do not fit in all aspects into that part of the physiologic picture of mitral regurgitation which is adequately documented.

The observations which follow are the result of studies performed upon 128 patients having "pure" or significant mitral regurgitation and stenosis. All of these have had right heart catheterization; 22 have had left atrial puncture.[27,28,37,63] Fifty-eight patients have been operated and in 56 cases hemodynamic studies have been carried out at surgery before and after correction of the mechanical defect.

Experimental studies have been carried out in the laboratory to investigate numerous physiologic and surgical problems of mitral regurgitation[22,60,61,64] and wherever useful these data will be utilized.

Summary of Pressure Pulse Changes Due to Mitral Insufficiency

The most dramatic alterations following the acute production of mitral regurgitation as well as in the chronic states, both in the experimental animals and in patients, are seen in the left atrial pressure pulse tracing. These are shown in Figure 1 where the aortic, left atrial and left ventricular pressure pulses are correlated and normal and abnormal characteristics compared.

The changes in left atrial pressure consist of a sharp rise in the peaks of the A and V waves, particularly the latter, in which case the peak is reached late in systole* or even in protodiastole. There is also a significant rise in mean pressure, particularly mean systolic pressure. The atrial minimum pressure may remain unchanged or may occasionally rise. The mean diastolic and the end-diastolic pressure levels will most frequently approximate closely the respective left ventricular pressures.

The changes in contour of the left atrial pressure pulse curve consist primarily of disappearance of the down slope following the C wave with a steep and often saw-toothed rise to the V peak. It will be noted that this rise begins at the C wave and is, therefore, initiated early in systole. The descending limb of the V wave (Y descent) drops sharply early in diastole. During the latter part of diastole, to the "A" wave in normal sinus rhythm or to end-diastole in auricular fibrillation, there may be a slight ascendancy of the curve.

The left ventricular pressure varies from normal in that the systolic peak, the systolic mean, and the mean pressures are decreased. The end-diastolic pressure may remain unchanged or may rise slightly in the acute experiment, but consistently shows some elevation in the chronic preparation. In patients with advanced disease, the end-diastolic pressure is invariably elevated to some degree, sometimes very markedly. In our view, this finding has assumed great clinical significance.

One feature of the *left ventricular pressure pulse curve* not previously described is the change in contour at the peak. This consists of a decline which begins early in systole and is associated with a very short maximal ejection phase.* The relationship of this pressure fall is evident in the studies of transvalvular systolic gradients which will be discussed later. The over-all length of systole appears decreased in view of the shortening of the isometric contraction phase and apparently also of the total ejection phase (although by Wiggers' criteria, the latter is of insignificant magnitude). Frequently there is also a shortening of the cycle length (increased heart rate), primarily at the expense of diastole.

The aortic pressure pulse exhibits relatively few changes. These are chiefly reduction of peak systolic, systolic mean, and mean pressures although the diastolic pressure in acute experiments also falls slightly. In patients the "blood pressure" is found to be normal or low. It is frequently decreased in the advanced stages of the disease. Arterial pressure tracings follow this trend.

Plots of the ventriculo-aortic systolic pressure gradient show that the interval during which there is a measurable positive difference is shortened in mitral insufficiency (vide infra).

The pulmonary artery pressure pulse shows changes in pressure and not in contour. Very frequently in the author's acute experiments systolic, diastolic, and mean pressures have been elevated. In symptomatic patients, pulmonary artery pressures are almost always elevated.

* The term systole, wherever used, refers to ventricular systole.

* The phases of the cardiac cycle are defined according to Wiggers.[61]

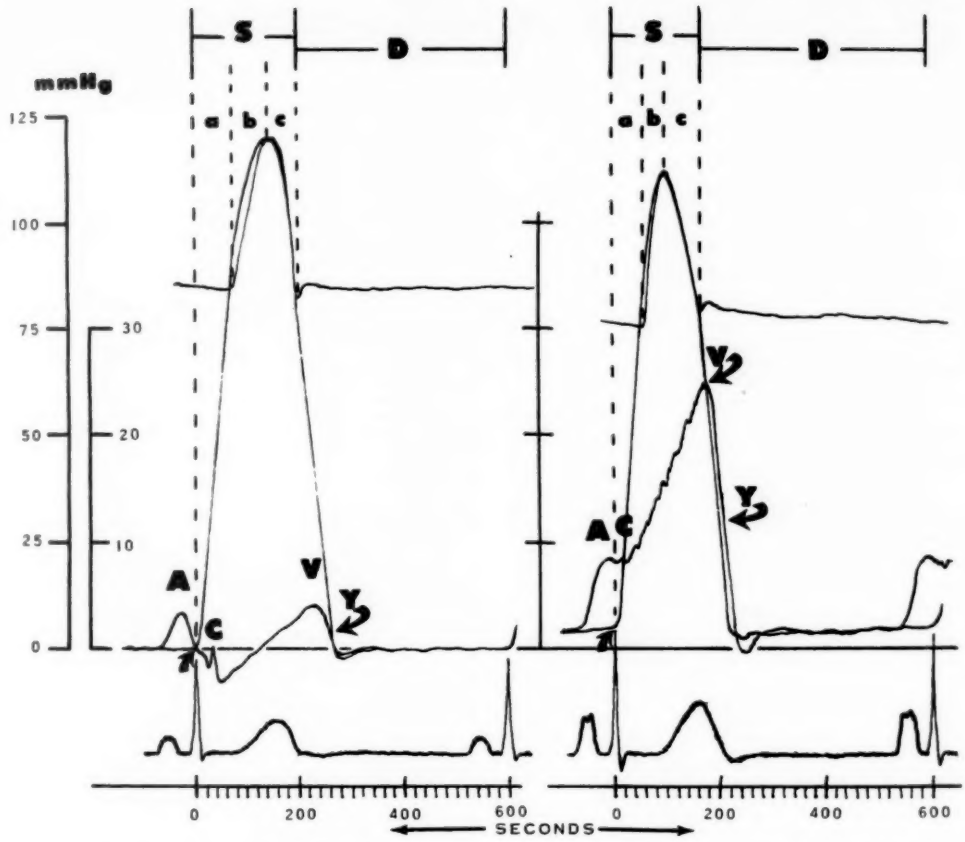

Fig. 1. On the left are diagrammed the normal aortic, left ventricular, and left atrial pressure pulses. The larger scale on the left corresponds to the aortic and ventricular pressures; the more sensitive scale is for the atrial pressure.

The characteristic features of the atrial curve are labeled. The A wave is the result of atrial contraction. The C wave is believed to represent mitral valve closure. The V wave is the result of pressure build-up due to atrial filling. The Y descent represents emptying of the atrial content into the ventricle in early diastole. At the bottom of the diagram is the ECG. At the top S indicates systole and D diastole. The intervals *a*, *b*, and *c* are, respectively, isometric contraction phase, maximal or rapid ejection phase, and reduced ejection phase.

On the right is a diagram of the same pressure pulses as altered by severe mitral regurgitation. The symbols indicate the same characteristics as in the normal diagram. Note in the atrial curve the elevation of all peaks, the loss of emphasis of the C wave, the absence of a decline following the C wave, and the sharp jagged rise to the V peak. Note also the position of V in protodiastole and the sharp Y descent. In the ventricular curve note the elevation of end-diastolic pressure (marked by arrows), the change in duration of the isometric contraction and ejection phases, and the drop-off during reduced ejection which begins earlier in systole at the end of the shortened maximal ejection phase. Note also the decreased peak ventricular and aortic pressures.

In our experience the highest pulmonary artery pressure observed (120 mm Hg) has been found in two cases of mitral insufficiency.

The pulmonary venous capillary pressure pulse may sometimes be equivocal due to artifacts or technical deficiencies which are unavoidable in certain instances. Nevertheless, it usually closely resembles the left atrial pressure pulse (Fig. 2).

Changes in Pressure Pulses Following Surgical Correction of Mitral Regurgitation

Following corrective surgery in animals and in patients all of the abnormal characteristics described are reversed toward normal.[22–26] The most striking reversal is observed again in the left atrial pressure pulse tracing. In a few clinical cases, an extremely abnormal tracing

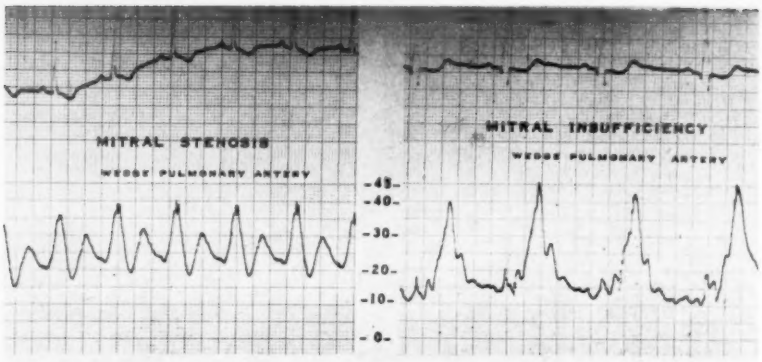

Fig. 2. Tracings of pulmonary venous capillary (or "wedge" pressure) to compare that of mitral stenosis (left) with that of pure mitral insufficiency in two cases with normal sinus rhythm. On the left the sharp peaks are A waves; on the right they are V waves.

has reverted to an essentially normal appearance (Fig. 3, 4). Occasionally an exaggeration of the

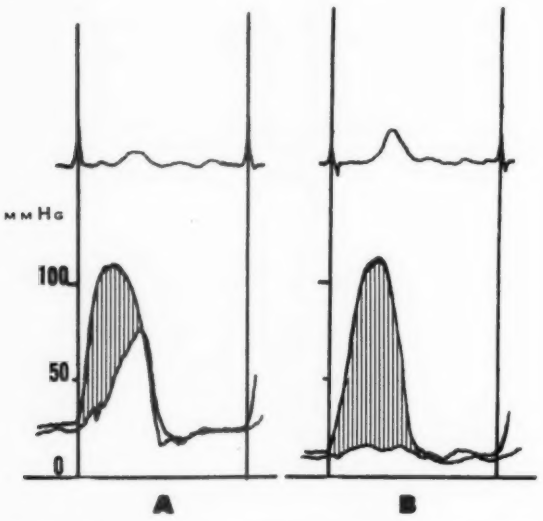

Fig. 3. Records taken at surgery, on separate channels, in the case of a patient with massive regurgitation, traced so as to superimpose the left atrial and left ventricular pressure pulses. The ECG is above. (A) Before correction of regurgitation. (B) After correction of the lesion by circumferential suture. Note the change in contour of both ventricular and atrial curves to a "normal" configuration (atrial and ventricular pressure scales are identical in both instances). Note the drop in left ventricular end-diastolic pressure and the slight rise in systolic peak. The shaded area represents the ventriculo-atrial systolic gradient.

C wave has been noted, particularly in experimental animals.

In most cases, the left ventricular end-diastolic pressure falls as would be expected. In some cases, however, there has been an elevation of this parameter.[26] This is an alarming phenomenon and appears to be of great importance.

It is almost routine to find marked reversal in the derangements in duration of the phases of the cardiac cycle and in heart rate as well as in the contour of the left ventricular pressure pulse.

There has been no significant change in the atrioventricular diastolic gradient in pure mitral insufficiency.[26] Ventricular and aortic systolic, mean, mean systolic, and aortic diastolic pressures rise in the majority of cases, although in some cases these pressures have shown little change after surgical correction. It seems likely that uncontrolled surgically induced changes in blood volume and vascular "tone" could account for the occasional failure of these pressures to rise.

In animals and in all but two cases of this surgical series there has been an elevation of the ventriculo-atrial systolic gradient.

Summarizing then, we find that the presence of mitral regurgitation causes certain very specific and characteristic alterations in the pressure pulses of the left atrium, left ventricle, and pulmonary venous capillary, and some nonspecific changes in the aortic and pulmonary artery tracings. Correction of the lesion usually reverses all these changes. The significance of these observations is of considerable deductive value, but this is greater when other parameters are taken into account.

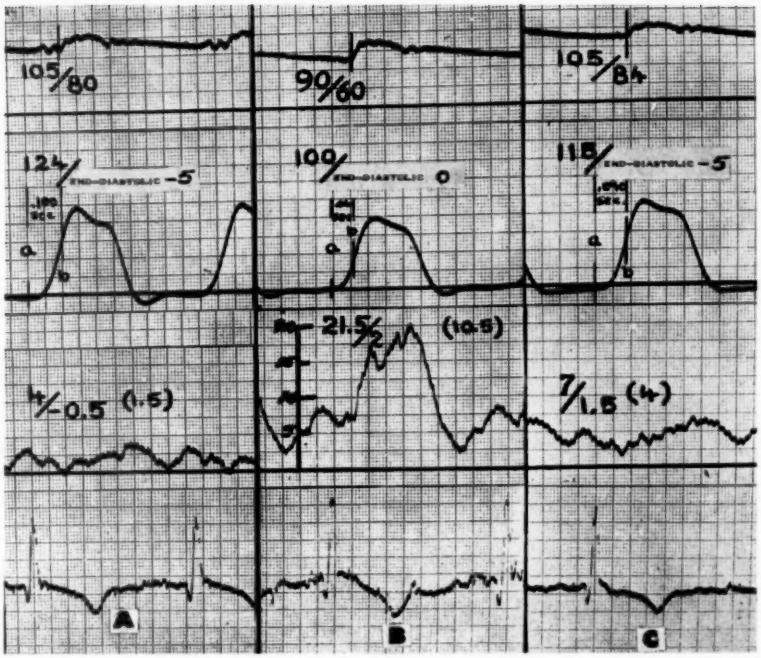

Fig. 4. From top to bottom are shown the aortic, left ventricular and left atrial pressure pulses, and the ECG as recorded in an acute experiment in a dog. (A) Control. (B) After production of mitral regurgitation by lacerating the mural leaflet of the valve. (C) After correction by circumferential suture. Note the return of all pressure pulses nearly to the control levels and appearance. Also note the changes in isometric contraction time (intervals labeled a-b) and in ventricular end-diastolic pressure.

Mitral and Aortic Transvalvular Gradients

In a hydraulic system there is a pressure drop downstream related to the degree of resistance, the rate of flow, and the upstream head of pressure (an extension of Poiseuille's law). This physical principle has been applied in the evaluation of stenotic valvular lesions, culminating in the development of a method for estimating the areas of obstructed mitral and aortic valves.[66–68] Unfortunately, the principle cannot be applied quantitatively where combinations of stenosis and regurgitation exist due to the present impossibility of estimating regurgitant flows with any degree of reliability.

To the author's knowledge, no attention has been paid to the reverse transmitral systolic gradient in regurgitant lesions* and little attention to the evaluation of the normal transaortic systolic gradient.

The observations presented here are based on the operative studies carried out on 40 patients, as well as the analysis of records from 20 acute experiments in animals.

The Transmitral Gradients

In the normal state, it has been universally found that there is no significant atrioventricular diastolic gradient although there exist normally small pressure differences at various points in the diastolic portion of the cycle.

In stenosis, the atrioventricular diastolic gradient has been recognized to have considerable importance as an index representing the degree of obstruction. When "pure" regurgitation exists, no elevation of the diastolic gradient should occur. In the majority of cases this is true. However, in our experience[26] and in that of Harken,[69] there has been a small incidence of gradient elevation (above 10 mm Hg) in

* Except for mention in passing of the relationship of ventriculo-atrial difference to regurgitation in the isometric contraction phase by Wiggers.[30]

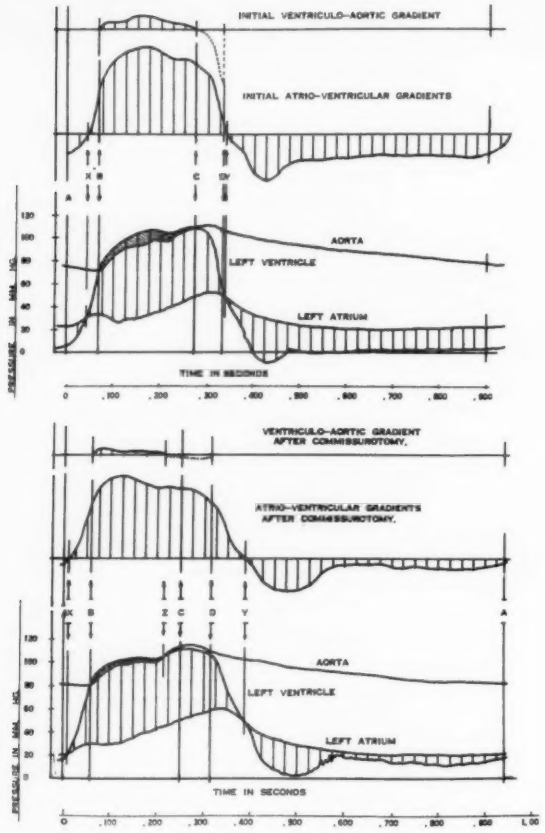

Fig. 5

Fig. 5. Left atrial, left ventricular, and aortic pressure pulse tracings were made before and after commissurotomy in a case of mitral stenosis with regurgitation. The records were made at paper speeds of 100 mm/sec. Gradients in systole across both aortic and mitral valves and in diastole across the mitral valve were plotted and are appropriately labeled.

The cycle intervals are labeled as follows: A to A: the complete cycle; A to B: isometric contraction phase; B to C: maximal or rapid ejection; C to D: reduced ejection; A to D: systole; D to A: diastole.

The points X and Y mark the duration of positive or negative gradient across the mitral valve. Commissurotomy in this instance significantly decreased the atrioventricular diastolic gradient, but increased regurgitation is evident.

Initially a positve ventriculo-aortic gradient was present throughout the maximal ejection phase (interval B-C). The ventriculo-atrial systolic gradient was high and reached its peak midway in maximal ejection phase. The diastolic atrioventricular gradient was quite prominent. Note the low initial ventricular end-diastolic pressure (at the intersection of line A).

After commissurotomy aggravation of regurgitation led to a shorter isometric contraction phase (A-B); lower systolic ventriculo-atrial gradient reaching a peak earlier in the maximal ejection phase and extending into early diastole (X-Y); lower and shorter ventriculo-aortic systolic gradient (B-Z). There is also a further elevation of the atrial V peak as well as elevation of ventricular end-diastolic pressure.

Estimates of relative regurgitant volumes in each cycle phase are shown in Table I. From the clinical standpoint this was an unsatisfactory surgical result, but the records obtained serve to illustrate the changes caused by acutely aggravated regurgitation.

cases with severe mitral regurgitation. This can be explained only as a "relative" stenosis due to the increase in forward flow across the valve as a result of the large regurgitant flow. The "effective" valve orifice which may handle normal flows without determining a gradient is, under ordinary circumstances, not likely to be large enough to admit forward flows of as much as four or more times the normal[26,64,70] without determining a pressure difference.

Perhaps more important than the diastolic gradient in proved mitral regurgitation is the ventriculo-atrial systolic gradient. In every instance in which regurgitation has been produced or corrected, there is a definite reciprocal change in this measurement. Normally the ventriculo-atrial systolic gradient should be only slightly lower than the ventricular pressures at any given time in systole since atrial pressure, even at its peak, normally rises only a few millimeters of mercury. When regurgitation exists, however, atrial pressure increases and ventricular pressure falls. This dual effect on the gradient reduces it. Conversely, when regurgitation is corrected, atrial pressure falls and ventricular pressure rises, returning the gradient toward its normal pressure levels.

In some instances, even though reduction in atrial pressure may not have been impressive, a sharp rise in left ventricular pressure determines a consequent increase in the gradient. In other cases, when left ventricular pressure has not risen significantly, or may have even decreased slightly, a marked drop in atrial pressure determines a rise in the gradient.

Determination of Phasic Regurgitant Flow: In order to further exploit these measurements, let us consider the left heart as an "orifice-flowmeter." During regurgitation (systole) the "up-stream end" is the ventricle, the "orifice" is the valve, and the "downstream end" is the atrium. Since there is "to and fro" flow across the valve, we plot the pressure differences from the ventricular tracing to the atrial tracing on a

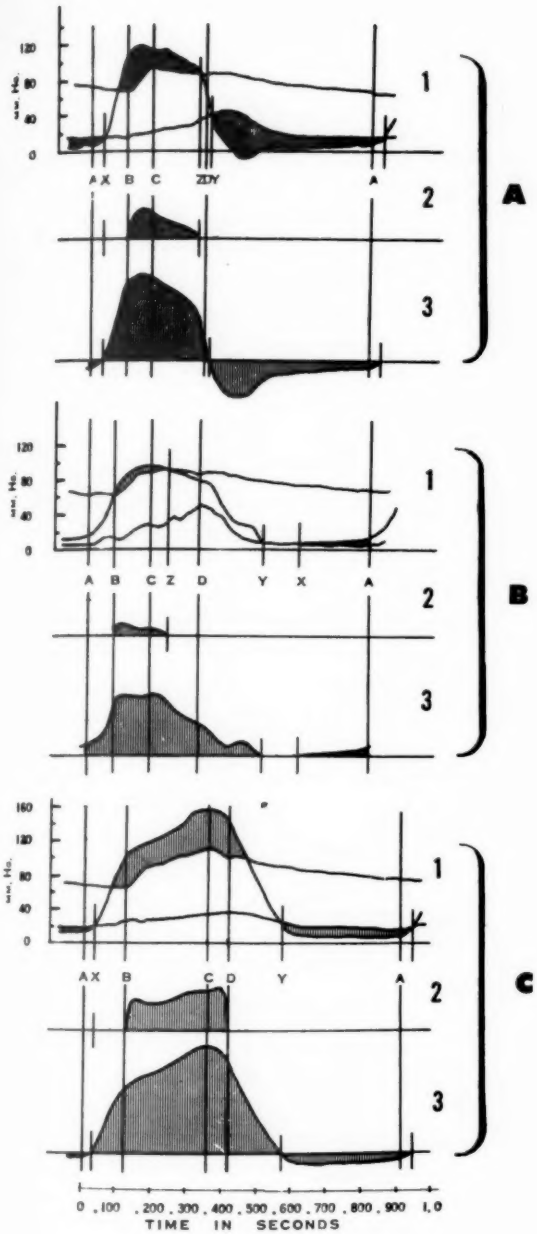

Fig. 6.

Fig. 6. Tracings of gradient plots from operation on a patient with massive mitral regurgitation, mitral stenosis, and aortic stenosis. A-1: initial tracings of aortic, left ventricular, and left atrial pressure pulses. A-2: plot of ventriculo-aortic systolic gradient. A-3: ventriculo-atrial systolic and diastolic gradient. Interval A-A is the full cycle; A-B is isometric contractions; B-C is maximal ejection; C-D is reduced ejection; A-D is systole and D-A is diastole.

In A-1 note the contour of the left ventricular curve in the ejection phases. Note also the respective lengths of the three phases of systole. Note the shape and levels of the positive gradient curve in A-3 as well as its duration (X-Y).

B-1 tracings taken after mitral commissurotomy. B-2 and B-3: plots of ventriculo-atrial systolic and diastolic gradients, respectively. Note how relief of the obstruction has abolished the diastolic mitral gradient. Aggravation of mitral regurgitation, however, has lowered ventricular and aortic pressure, raised atrial V peak pressure, shortened isometric contraction, reduced the height and duration (B-Z) of the ventriculo-aortic systolic gradient, reduced the height of systolic ventriculo-atrial gradient and emphasized its early peak as well as extended it into diastole (X-Y).

C-1: tracings after correction of regurgitation by circumferential suture of the mitral valve. C-2 and C-3 ventriculo-aortic systolic and ventriculo-atrial systolic and diastolic gradients, respectively. There is now an elevation of ventricular and aortic peak pressures and a reduction of atrial pressure. There is a prolongation of isometric contraction and a marked shift in the position of the ventricular pressure peak with an extended maximal ejection phase. Note in the gradient plots the elevation and prolongation of the ventriculo-aortic systolic gradient (B-C) and also the elevation and shift of the peak to late systole in the ventriculo-atrial systolic gradient.

The ventricular end-diastolic pressure rose to 20 mm Hg after commissurotomy but fell to 14 mm Hg after correction of the regurgitant lesion despite an increase in ventriculo-aortic gradient. The effects of even minor degrees of aortic stenosis associated with mitral insufficiency can be accentuated by correction of the mitral lesion.

Estimates of fractional regurgitating volumes are given in Table I. Despite multivalvular disease and only partial relief of mitral regurgitation this patient has had an uneventful postoperative history, is well and active two years after surgery.

zero line with a positive deflection for systolic difference and a negative deflection for diastolic difference, obtaining a curve, the area of which quantitatively represents flow at a given valvular resistance. We may call this a "phasic flowgram" (Fig. 5, 6, 7).

Because we cannot measure the area of the valve orifice either in systole (regurgitant) or diastole (effective) nor at any moment of the cycle (Fig. 8), we cannot calculate flow in volumetric units. It is obvious, however, that *all* the forward flow crosses the valve during diastole when the gradient favors the atrial side, and all the regurgitant flow crosses back when the gradient favors the ventricular side, most of it during systole.

We can consider, then, that the systolic (positive) area of the flowgram curve represents 100 per cent of the regurgitated volume. By comparing fractional areas, corresponding to each cycle phase, to the total we can estimate

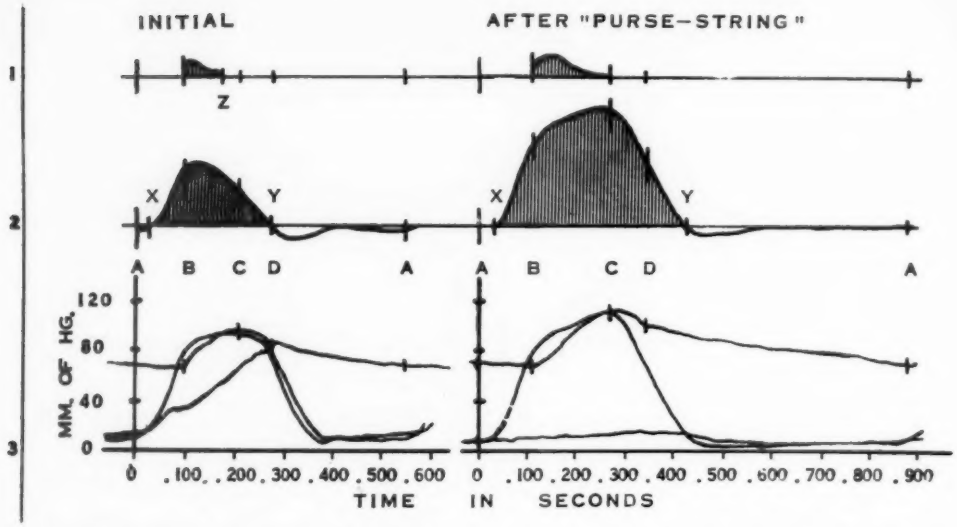

Fig. 7. Flowgrams of aortic and mitral valves (1 and 2) taken from operative tracings in a patient with pure massive mitral regurgitation corrected by surgery.

The cycle phases are labeled: A-B: isometric contraction; B-C: maximal ejection; C-D: reduced ejection; D-A: diastole; A-D: systole; Z: end of ventriculo-aortic gradient; X-Y: duration of ventriculo-atrial gradient.

Note the extreme elevation of atrial peak pressure and the low aortic and ventricular pressures as well as the elevated ventricular end-diastolic pressure (intersection of line A). These parameters were all reversed to normal or nearly so. The changes in contour, duration, and level of the gradients are discussed in the text. Estimates of relative regurgitant flows in each cycle phase are given in Table I.

This patient had a ruptured chordae tendineae. A highly satisfactory mechanical correction was achieved[92] and his postoperative course has been one of dramatic improvement, lasting to the present time (22 months postoperatively).

what percentage of flow regurgitates in each phase, disregarding moment-to-moment changes in valvular orificial size (resistance) during systole (see Table I). This would appear to be a more meaningful measurement of phasic regurgitation than that based only on the atrial pressure pulse,[30] since the latter reflects the cumulative regurgitated volume rather than the moment-to-moment *regurgitating* flow.

Estimates made in this manner are in accord with Wiggers' deduction[30] that only a small fraction of the total regurgitates during isometric contraction. However, it appears that this fraction can increase to significant proportions in advanced states. The largest volume regurgitates during the maximal ejection phase, although when this is very short (Fig. 6), maximal regurgitation may occur in the reduced ejection phase. These observations suggest that the pressure limits of the flowgram curve, its contour, fractional areas, and the length of the base are of significance in evaluating degrees of regurgitation.

The three cases illustrated in Figures 5, 6, 7 are typical. We can assume from direct palpation of the valves and from the pressure pulse tracings that regurgitation is greater after commissurotomy (Fig. 5, 6) and less after the "purse-string" operation (Fig. 6, 7). After aggravation of the regurgitation, the pressure level of the flowgram curve decreases, there is a definite shift of its peak to a position earlier in systole and there is a lengthening of the base extending into diastole. Following correction of regurgitation, there is a marked rise in pressure level and a sharp shift of the peak into later systole. The base, although sometimes still wide, is shortened relative to diastolic length.

THE VENTRICULO-AORTIC GRADIENTS

From the beginning, it is admitted that measurement of the ventriculo-aortic systolic gradient, in the absence of aortic stenosis, is a difficult technical problem at best. The consistency in direction of the changes observed in patients and in animal experiments, however, lends

TABLE I

Calculations of Regurgitant Flow During Various Phases of the Cardiac Cycle Before and After Surgical Correction

Case illustrated in figure	Phase	Before		After commissurotomy		After "purse-string"	
		Area	%	Area	%	Area	%
5	Total area (regurgitant)	6.7	100.0	7.3	100.0	—	—
	Isometric contraction	.15	2.3	.4	5.5	—	—
	Maximal ejection	5.1	76.0	5.0	68.5	—	—
	Reduced ejection	1.4	21.0	1.4	19.2	—	—
	Protodiastole	.05	.7	.5	6.8	—	—
6	Total area (regurgitant)	2.2	100.0	2.2	100.0	4.4	100.0
	Isometric contraction	.3	13.6	.3	13.6	.2	4.5
	Maximal ejection	.8	36.4	.8	36.4	2.6	59.0
	Reduced ejection	1.0	50.0	.8	36.4	.8	18.25
	Protodiastole	.01	.1	.3	13.6	.8	18.25
7	Total area (regurgitant)	1.9	100.0	—	—	6.2	100.0
	Isometric contraction	.4	20.3	—	—	.68	11.0
	Maximal ejection	1.26	67.0	—	—	3.52	56.9
	Reduced ejection	.24	12.7	—	—	1.52	24.5
	Protodiastole	0	0	—	—	.48	7.6

For interpretation of this table refer to Figures 5, 6, and 7. The areas are in cm^2. The percentage refers to percentage of total regurgitated volume in each of the phases of the cardiac cycle listed.

some significance to the findings to be described.

Normally the aortic valve should offer minimal resistance to ventricular ejection. However, even if the valve did not exist, and the outflow tract of the left ventricle were a straight tube, there would be a pressure drop "downstream" (according to Poiseuille's law). The outflow tract is at best a cone and the valve does exist; therefore, in order that forward flow be possible, the existence of a gradient, small as it may be, must be postulated.

Careful examination of superimposed aortic and ventricular curves (more recently recorded from a multichannel oscilloscope with a camera) reveals that this gradient involves a time-pressure relationship. In the absence of aortic stenosis there is no measurable difference in most instances at the peak ventricular and aortic pressures. However, from moment to moment, particularly during the rapid ejection phase, there is a difference.

Again applying the concept of the orifice-flow-meter an aortic valvular flowgram can be plotted. In Figures 6 and 7 these measurements determine a positive gradient which initially lasts the full length of the maximal (rapid) ejection phase in one (Fig. 5) and about two-thirds of that length in the other. After aggravation of mitral regurgitation there is a significant shortening of this interval (Fig. 5) and even though the maximal ejection phase is reduced the duration of the gradient is even shorter. This phenomenon is better shown in Figure 6 where some degree of aortic stenosis coexisting with mitral stenosis and regurgitation emphasizes the point. Here the gradient is initially measurable, nearly but not quite, to the end of systole. When mitral regurgitation is aggravated its duration is markedly shortened. After correction of mitral regurgitation there is an elevation in pressure as well as a prolongation of the gradient interval to the end of systole.

Further evidence indicating the changes in the interval during which forward flow can occur is available from cinematographic records of valve action made on the pulse-duplicator.[64,70] The number of frames in which each valve is open and closed can be counted and the result compared under various circumstances at a constant pulse rate and film speed. The aortic valve remains open a longer period of time (a greater number of frames) when the

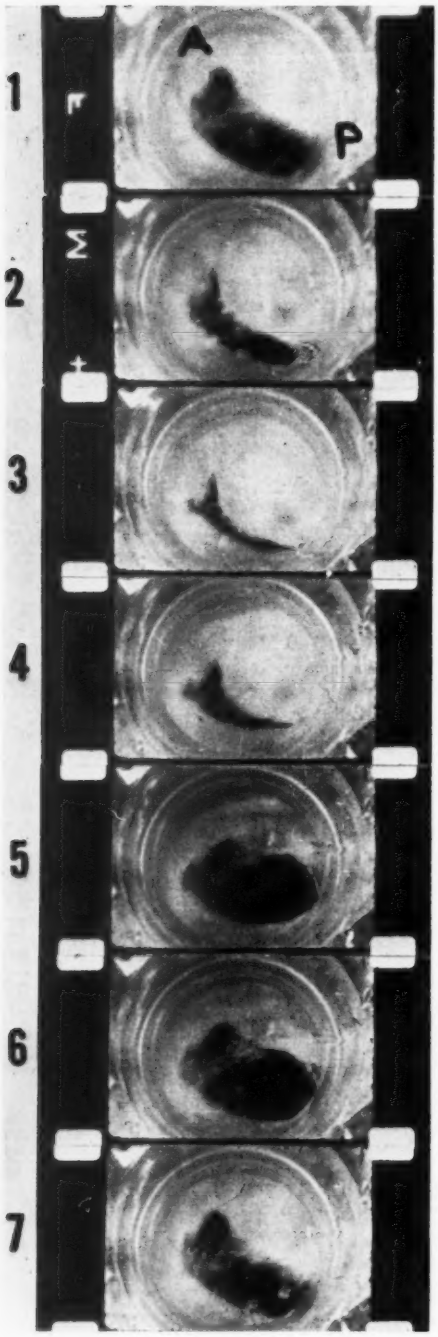

Fig. 8. Moving picture record of an incompetent mitral valve made on the pulse duplicator. Frames numbered 1, 2, and 3 are systole. The cycle actually lasts through 14 frames, but for illustrative purposes alternate frames have been deleted. Note that the valve orifice is larger early in systole (frame 1) . . . . the valve does not "snap" to a closed position, rather it "floats" toward that position. This serves to illustrate the variation of valvular regurgitant orifice resistance.

mitral valve is rendered competent by surgical manipulation.

Vascular Resistance

Total pulmonary resistances have been found to be surprisingly elevated in the vast majority of patients studied.[26] It is of interest that in mitral regurgitation the greatest elevation is seen in total pulmonary vascular resistance, and although pulmonary arteriolar resistance is increased, it is not often as high as that seen in mitral stenosis. The study of 34 lung sections obtained by surgical biopsy and at autopsy has shown a relatively low incidence of definite pulmonary arteriolar sclerosis (four cases). There has been a slightly higher incidence (seven cases) of interstitial fibrosis which may have some bearing on pulmonary vascular resistance.

Peripheral arterial resistance does not seem to be significantly altered in the patients studied. This would imply that vascular tone adjusts to the decreased cardiac output to maintain reasonable, if lower, tissue perfusion pressures.

It is of interest to note here that the use of vasopressor agents in surgery, when a patient under anesthesia requires circulatory support, is associated with very variable responses. In advanced cases it is extremely difficult, if not impossible, to restore the peripheral blood pressure. Indeed, it is our impression that in such cases, the use of these agents is contraindicated. Pressures in the pulmonary artery and left atrium considerably higher than those recorded in the preoperative studies have been observed at surgery in some cases in which such drugs were used.

Cardiac Output—Ventricular Volume—Regurgitant Flow

The cardiac output has consistently been found to be reduced in patients with serious mitral regurgitation.[26] In fact, in adults where one could expect an output of four or five liters per minute, cardiac outputs as low as 1,200 cc/min have been found. In patients, measurements immediately after correction of the lesion (vide infra), and up to 12 months after surgery, show significant increases in cardiac outputs.

Dye Dilution Technics

Experiments using Evans blue dye (T-

1824)[71–81] have been conducted in the laboratory and in patients at the time of surgery in attempts to measure regurgitant flow. Others have applied indicator dilution technics to this problem in several ways.[82–85] Our interest has centered about the use of serially injected dye into the left ventricle, left atrium, and proximal ascending aorta[26] in the hope that by quantitation and analysis of these curves mitral regurgitant flows might be calculated (Fig. 9).

Regurgitant Flow and Ventricular Volume: In theory, if we were to assume thorough mixing of blood and dye, complete emptying of the left ventricle in systole, and a negligible constant influence of the coronary flow fraction, it would be possible, by calculating dye dilution in the aortic injection and comparing it to that of the ventricular injection, to say that the increase in ventricular dilution represented regurgitant flow. In fact, there is good evidence[86–90] that ventricular emptying is not complete even in the normal state. In mitral insufficiency, the major compensatory mechanism is that of ventricular dilation. This presumably determines an increase in residual left ventricular volume. Coronary flow is generally thought to represent as much as 10 per cent of cardiac output. Under actual circumstances, then, calculation of the regurgitant flow by the method alluded to would require a separation of the difference between aortic and ventricular dilution into fractions representing regurgitant flow, ventricular residual volume, and coronary flow. This is not possible by current methods. In addition, the moment-to-moment changes of circulatory functions probably affect each of the serial injections differently.

The determinations carried out in nine acute and four chronic experiments in the laboratory and in 20 patients at the time of surgery have nevertheless indicated some interesting possibilities (Fig. 9). It must be stated that dye studies under these conditions are subject to several sources of error which are difficult to eliminate. This is particularly true in the studies carried out on patients at surgery where recordings have been made with the use of an earpiece rather than a cuvette, and are therefore subject to greater problems in calibration. The measurements, however, are relative to each other in any given case, and thus are comparable to some extent.

Calculations of forward flow show consistent increase immediately after correction of mitral insufficiency. It has been noted incidentally that cardiac outputs determined at surgery by this method have been in fair agreement with those determined by the Fick principle at right heart catheterization.

The estimates of total left ventricular volume before and after correction have shown variable behavior. In some instances there is a decrease which would indicate decrease in either or both regurgitant and residual volumes, assuming that coronary flow does not increase significantly. In others there has been an increase which, in the presence of increased forward flow and an increased ventriculo-atrial gradient signifying a decrease in regurgitant flow, would imply a significant increase in residual volume. In still others there has been little change, but again, in the presence of increased forward flow and increased ventriculo-atrial gradient implying a reduction in regurgitant flow, there would appear to be a relative increase in left ventricular residual volume (Fig. 9). There has been some correlation of these determinations with the radiologic estimate of heart size. The reliability of these measurements has not been fully evaluated in terms of technical accuracy, and much less, of clinical significance. Conclusions in this regard must await further technical refinements, experience, and analysis.

The Work of the Heart

The data described in the preceding section, despite their shortcomings, allow a preliminary perusal of changes in myocardial work associated with the existence of mitral regurgitation and following its mechanical correction. Calculations of the work of the left ventricle on the basis of measurements of forward flow alone (cardiac output) are in agreement with the suggestion originally made by Barry[51] that in mitral insufficiency the work of the heart is decreased; this seems to be particularly so in advanced cases. Similar estimates following correction of the lesion by circumferential suture consistently show an increase in left

ventricular effective or useful work (increased forward flow and increased aortic and ventricular pressures).

Estimates of right ventricular work have not been made and thus total useful work of the heart cannot be discussed here. On the basis of available data "useful" work of the right ventricle can be speculated upon and will be briefly mentioned later.

The calculation of useful cardiac work does not render a true picture of the actual load imposed upon the myocardium, particularly in

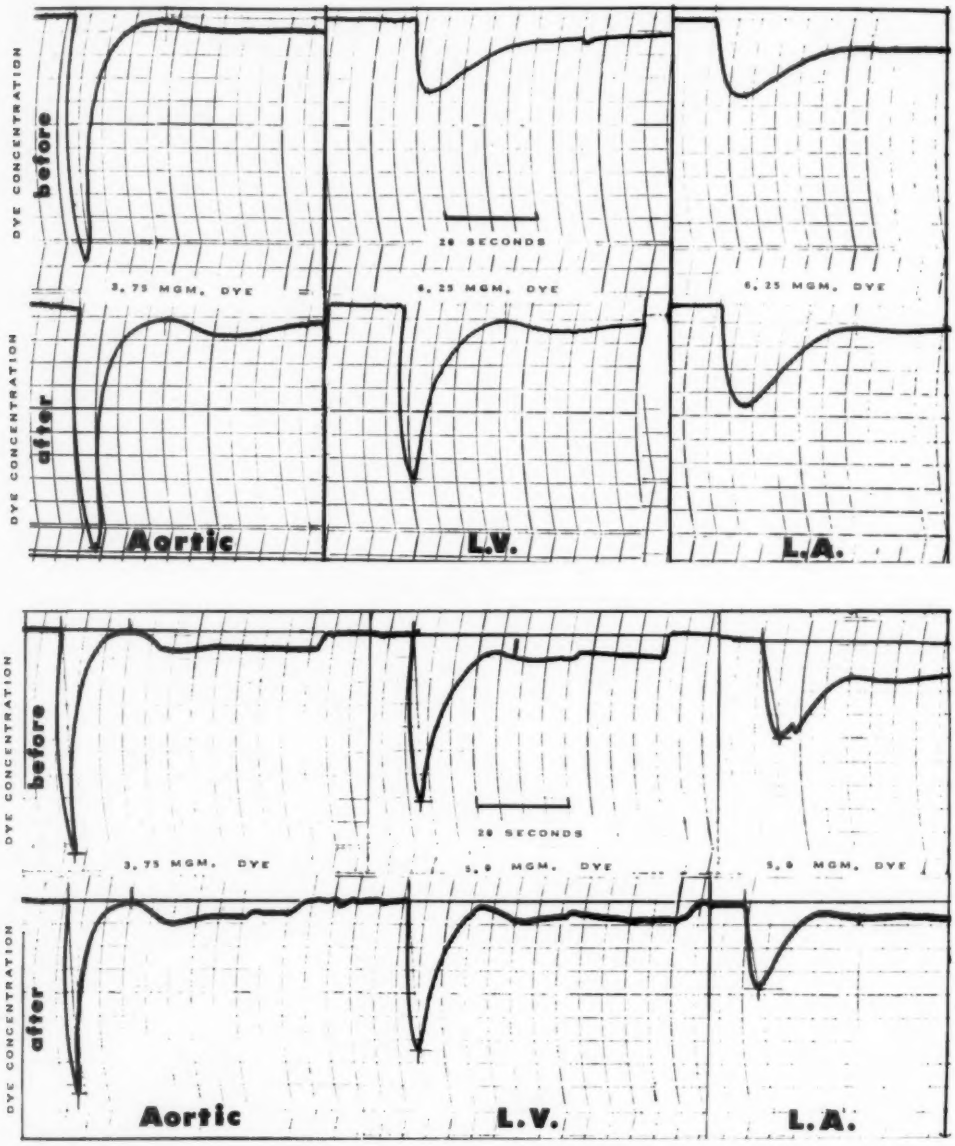

Fig. 9. Two sets of serially recorded Evans blue dye curves. A Waters ear-piece oximeter and a Grass recorder were used. Dye was injected at operation into the ascending aorta, the left ventricle, and the left atrium in sequence. During the series the patient was ventilated with pure oxygen using a mechanical respirator. A set of tracings was made before and another after correction of regurgitation. Pressure tracings in both cases showed marked changes toward reduction of the regurgitant defect similar to those illustrated in the previous figures. Digital palpation also corroborated the indication of marked reduction of regurgitation.

The cardiac output can be calculated from each curve by Hamilton's method (calibration in these studies was accomplished by determination of dye content in blood taken at known deflections on the record). This measurement

represents forward flow. Theoretically, if there were no residual volume and no regurgitation, and if one disregarded coronary flow, all three serially obtained curves would be identical. Because of incomplete mixing, minute variations in injection rate and amount of dye delivered, as well as unavoidable error in measurement of the recorded tracing, the agreement in the cardiac output determinations within any given series of injections is in the realm of 10 per cent at best. For these reasons the results of these determinations cannot be regarded as incontrovertible. Nevertheless, the consistency of direction of the changes observed lends some strength to the possible significance of the study.

The major variations in time-concentration relationship among the three curves in a given series are due to the influence upon dilution of ventricular and atrial volumes and to regurgitant flow. Residual ventricular volume and mitral regurgitant volume are manifested in the lowered peak dye concentration and mean dye concentration values as well as in the prolongation of dye-passage time and of build-up time. It can be assumed that these factors are proportional (theoretically) to the magnitudes of existing residual and regurgitant volumes. Based on this premise the sum of these two values can be estimated by a simple arithmetical proportion using any one of the four factors listed above. Use of combinations of these factors can also be postulated. (For example: an index obtained by relating dye build-up time and maximum concentration.) However, since "dye-passage time" is already a factor in the Hamilton formula, since it is numerically easy to handle, and since the results are of comparable consistency, the use of this factor has seemed practical.

Where: Dmao = mean dye concentration of aortic curve; Dmlv = mean dye concentration of left ventricular curve; Tao = dye-passage time of aortic curve; Tlv = dye-passage time of left ventricular curve; Qs = forward flow; Qrlv = ventricular residual volume; Qmr = mitral regurgitant volume;
The equation:

$$\frac{Qs}{Tao} = \frac{Qs + Qrlv + Qmr}{Tlv}$$

can be solved as follows:

$$(Qrlv + Qmr) = \frac{Tlv\,(Qs) - Tao\,(Qs)}{Tao}$$

If in addition: Slv = left ventricular stroke volume; Pmslv = left ventricular mean systolic pressure; Wlv = left ventricular work; SWlv = left ventricular stroke work; F = heart rate, by substituting the numerical values in the right side of the equation a figure is obtained which represents an estimate of the sum of left ventricular residual volume and regurgitant volume. We can then obtain *total stroke volume:*

$$Slv = \frac{Qs + Qrlv + Qmr}{F}$$

If left ventricular pressure pulse tracings are taken at the time of injection mean systolic ventricular pressure can be calculated planimetrically. This figure is used here to represent the force necessary to overcome the resistances offered against ventricular ejection. Thus, *left ventricular stroke work* can be estimated:

$$SWlv = (Slv)\,(Pmslv)$$

By the proper conversions, this value can be expressed in kilogram-meters or in kg-M/kg of body weight or per meter of body surface. Applying these theories to the curves obtained in the above cases we find that in:

		Before correction	*After correction*
	Case A:		
	Qs	4070 cc/min	4438 cc/min
	Qrlv + Qmr	1580 cc/min	2462 cc/min
	F	84/min	72/min
	Slv	77.4 cc	94.6 cc
	Pmslv	1144 mm H_2O	1117 mm H_2O
then:	SWlv	.093 kg-m	.111 kg-m
or:	Wlv/min.	7.81 kg-m/min	7.98 kg-m/min
	Case B:		
	Qs	3000 cc/min	3515 cc/min
	Qrlv + Qmr	2115 cc/min	3305 cc/min
	F	114/min	102/min
	Slv	44.9 cc	67.0 cc
	Pmslv	930 mm H_2O	975 mm H_2O
then:	SWlv	.045 kg-m	.069 kg-m
or:	Wlv/min	5.18 kg-m/min	7.05 kg-m/min

Note: Coronary flow has been neglected in these estimates because its magnitude cannot be measured. It is included in (Qrlv + Qmr). If we assume that coronary flow is 10 per cent of Qs then this value would be subtracted from the value given above for (Qrlv + Qmr). In case A: Coronary flow = 407.0 cc/min before and 443.8 cc/min after. Respectively then: Qrlv + Qmr = 1173 cc/min; and: Qrlv + Qmr = 1918 cc/min.

regurgitant lesions where backward flow and residual volumes add to the total volume of blood "handled" by the heart. It is thus necessary to know the true or total ventricular stroke volume in order to arrive at a more meaningful estimate of total myocardial work.

The measurements described and illustrated in Figure 9 have been applied to this problem. Under ordinary circumstances there is no way of knowing what constitutes normal, low, or high values for total left ventricular work, since no precedent exists of measurements similar to those used here. However, there is a tendency for values to be lower in the more advanced cases of mitral insufficiency. Comparison of measurements made at surgery, before and after correction of the regurgitant lesion, indicates either a slight change or a definite increase in total left ventricular work as in the cases illustrated. If valid, these studies suggest, in opposition to the empirical view generally entertained, that relief of regurgitation will increase left ventricular work, at least under certain circumstances.

Discussion

Briefly, we may state that the changes which follow correction of mitral insufficiency are generally in the reverse direction of all the recognized hemodynamic derangements attributable to this valvular lesion. Furthermore, the degrees of change generally seem to be a reflection of the degree to which regurgitation has been reduced.

Two very important parameters fail, in some instances, to follow this trend. These are left ventricular end-diastolic pressure and total left ventricular volume. The importance of this observation is emphasized by the fact that this behavior is common in those cases in which the ultimate result, despite satisfactory mechanical relief of the valvular lesion,* was fatal at surgery or within a few months thereafter.[26] With this in mind, certain fundamental concepts of physiologic behavior of this disease may be re-examined.

* Favorable changes in left atrial pressure, pulse pressures and contours, left ventricular peak and mean pressures and curve contour, aortic pressure, favorable changes in duration of the cycle phases and in cardiac output, as well as favorable anatomic valvular changes detected at surgery and at autopsy.

Forward Left Ventricular Ejection and Compensatory Mechanisms

The explanation of why forward ejection is possible in mitral regurgitation has interested many workers. The hypothesis most widely accepted is that of Wiggers and Feil,[30] who, based on their demonstrations of consistent shortening of the "isometric contraction phase" and on the deduction that only minimal if any regurgitation occurred during this phase, stated that "enhanced" ventricular contraction indicated by the former, and residual directional inertia of atrioventricular flow, suggested by the latter, make possible continued forward flow in the presence of a leaky mitral valve. Furthermore, it has been thought that increased initial tension (end-diastolic pressure) or ventricular dilatation, is the determining factor of "enhanced contraction." This interpretation might be questioned in the light of the observations reviewed here.

Shortening of Isometric Contraction Phase: Does the shortened time interval between the beginning of electrical systole and the foot of the ascending limb of the systolic aortic curve indicate enhanced ventricular contraction? Does increased initial tension (dilatation) *per se* result in the shortening of that interval? Or is ventricular dilatation a consequence of the lesion which allows compensation within certain limits merely by augmenting its capacity so that forward flow can be maintained despite a large volume of wasted backward flow?

Myocardial contractility is only one of the factors which influence the duration of the phases of systole. Shortening of the isometric contraction phase could be attributed to a reduction of the resistance against which ventricular force is exerted. Wiggers minimizes the role of peripheral resistance changes in this regard, but even if peripheral resistance were unchanged, the existence of a regurgitant orifice represents a significant reduction in the total resistance against which the left ventricle works, by providing a low-pressure pathway for the ejection of blood. This can, in itself, determine a reduction in isometric contraction. An

analogous situation can be seen when peripheral resistance is reduced by administration of vasodilators or by other means (Fig. 9) which likewise result in shortening of the isometric contraction phase. Certainly, under these circumstances, no enhanced myocardial contraction due to dilatation can be postulated. Furthermore, mechanically increased or drug-induced increases in peripheral resistance are followed, in the presence of mitral valve competence, by prolongation of isometric contraction time as well as by ventricular dilatation. If the latter were the determinant of shorter isometric contraction, then the former could not occur.

The observed behavior of the "isometric contraction" interval is most likely due to the play of opposing expulsive and resistive forces. One may make an analogy by considering the effect of an opposite force upon the tension-build-up time of any mechanical force. The slope of the ascending limb of the force-time curve would be the mechanical resultant of the two. If no opposition were offered, a square wave would be generated, all other factors being equal.

Other Factors Influencing Ventriculo-Atrial Regurgitation Flow: Regurgitant flow must be determined by mitral orificial resistance as well as by the reciprocally changing ventricular and atrial pressures among other factors reflected in the ventriculo-atrial systolic gradient. These changes in atrial and ventricular pressures depend at any given time in the cycle, not only on valvular orificial size, but also on the cumulative *regurgitated* flow up to that point, and not on the momentary *regurgitating* flow. Thus, atrial pressure would be highest when the maximal amount of blood ejected from the ventricle has been accumulated in the atrium. At the same time, resistance to further regurgitation will be higher because of the elevated atrial pressure. Further regurgitation would be slowed by this opposing force as well as by the lowered ventricular pressure.

This interpretation of the evidence strongly suggests that significant degrees of regurgitation can occur early in systole (even during "isometric contraction") and that the only reason that forward ejection is possible is by virtue of the competitive magnitudes of mitral and atrial resistance on one hand and forward vascular and valvular resistance on the other. Indeed, on the pulse duplicator, where myocardial contractility is eliminated as a factor, it is possible without altering rate or stroke volume, to decrease mitral valvular regurgitant resistance to a point where no forward flow can occur; conversely, by progressively diminishing mitral regurgitation (i.e. increasing mitral valvular regurgitant resistance) forward flow can be increased.

Atrioventricular Flow Inertia: One must qualify the term "isometric contraction" by questioning whether this is possible in mitral insufficiency. If the hypothesis of atrioventricular flow inertia* is entertained one could, at least in part, support the view that no change in ventricular volume occurs in this phase of systole. However, it is clear from the atrial pressure curves and from ventricular volume curves[48,87,90] that the ventricle receives the atrial content early in diastole. The atrium appears to literally "dump" its content into the ventricle. In normal sinus rhythm atrial contraction can augment atrioventricular flow in the presystolic period and thus potentially set up an inertial factor as postulated. No such situation could conceivably occur in auricular fibrillation, where "end-diastolic pressure" is identical on both sides of the valve. Furthermore, if directional inertia were a significant factor, the fact that regurgitant flows greatly exceed forward flows should indicate that, in a reverse manner, the inertia of regurgitant flow would hamper left ventricular filling, particularly if maximal regurgitation occurred late in systole and early diastole. The sharp drop of the V wave (Y descent), ventricular volume curves, as well as the diastolic portion of the atrioventricular flowgrams indicate that the atrium empties rapidly early in diastole (even though regurgitation continues into protodiastole).

In this light, the existence of a gradient favoring ventriculo-atrial flow during the "isometric contraction phase" plus the fact that valvular orifice resistance is least (size largest) at this time would indicate that regurgitation does occur, and therefore, that ventricular volume

* Refers to the moment of inertia entailed in the arrest of forward flow, across the mitral orifice, late in diastole.

does change during this phase. However, from the flowgrams, it can be estimated that the percentage of total regurgitated volume moving in this interval is small, even though it may be greater than heretofore realized.

Summary of Compensatory Mechanisms: The evidence which leads to this reasoning appears to minimize the significance of changes in "isometric contraction" time alone as an indication of enhanced myocardial contractility in mitral regurgitation. Furthermore, there arises the question of whether there is a consistent correlation between changes in isometric contraction and initial tension since in the cases in which end-diastolic pressure rises when regurgitation is corrected, the duration of the phase in question is increased concomitant with reduction in regurgitation. There seems to be very little change in all parameters until regurgitation reaches rather large magnitudes. In Figure 4 there is only a slight change in end-diastolic pressure in the ventricle; in Figure 10 there is a marked rise in this parameter, particularly after a vasoconstrictor was given. In both there is marked reduction of the isometric contraction phase.

It seems more likely that compensation in mitral regurgitation depends not on improvement in myocardial contractility, but rather on the ability of the ventricular myocardium to

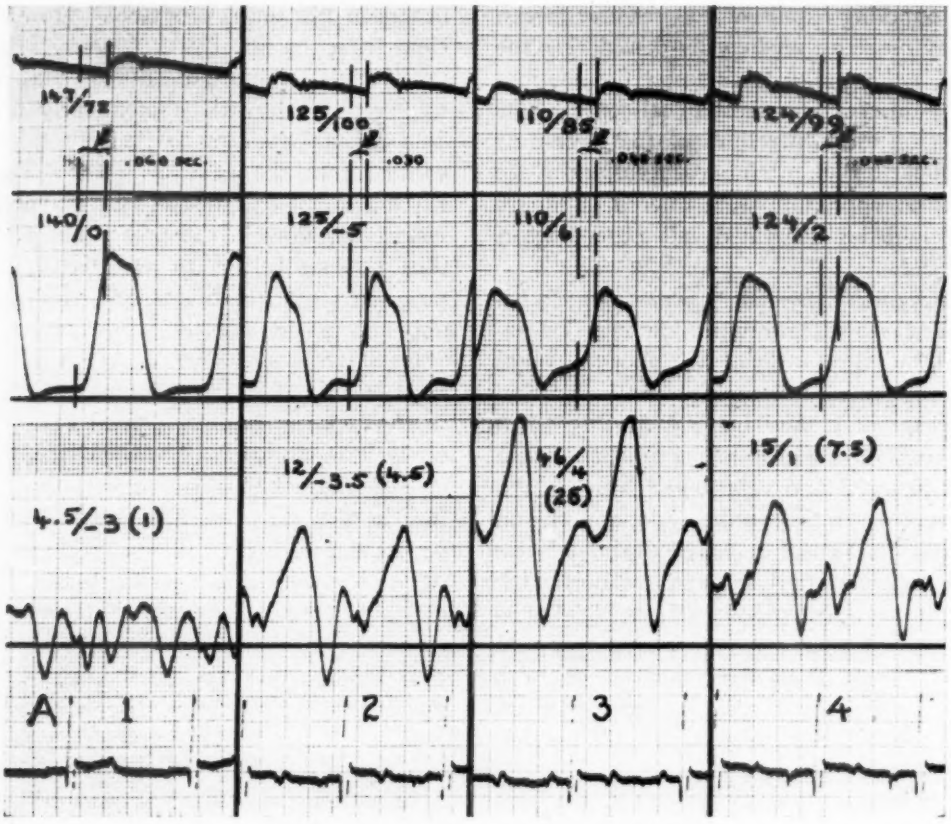

Fig. 10 A. Simultaneous tracings of aortic, left ventricular, and left atrial pressure pulses and ECG (from top to bottom) in an acute dog experiment. The pressures are noted on the record. Paper speed was 100 mm/sec. (1) control; (2) after laceration of the mural leaflet of the mitral valve to produce regurgitation; (3) within one or two minutes after administration of vasoxyl (methoxamine HCl); (4) fifteen minutes after the vasoxyl injection.

The changes described in Figure 1 are seen in stage 2 of this experiment. After the increase in peripheral resistance there is an aggravation of the regurgitant mechanism. Note, however, that despite this fact isometric contraction (arrows) is not further decreased; if anything it is slightly prolonged. In (4) after the vasopressor effect wears off there is no further significant change in this phase of the cycle.

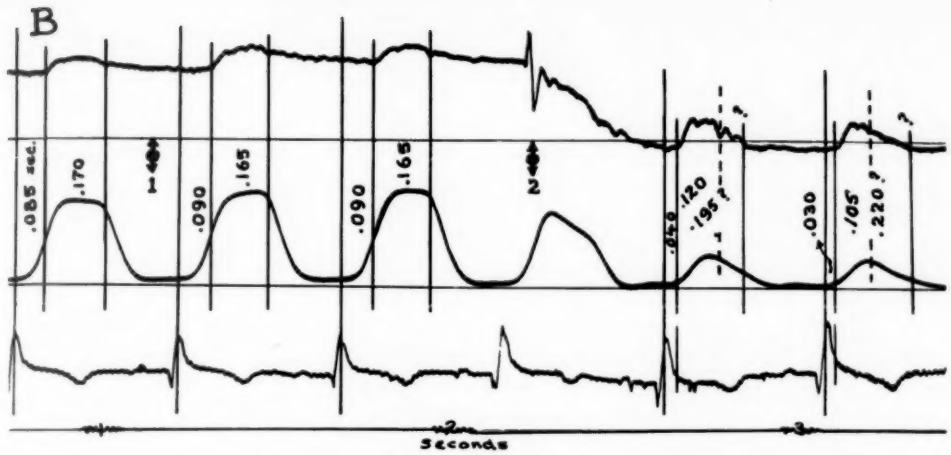

Fig. 10 B. Aortic and ventricular pressure pulses and ECG in another acute dog experiment. In order to produce the most drastic reduction in peripheral resistance possible, the ascending aorta was quickly transected (during the intervals marked by arrows 1 and 2 on the record). During the two beats immediately following point 1 the aorta was occluded by the closing scissors. Note the slight increase in isometric phase. Severance occurred at point 2. Note the marked change in duration of isometric contraction in subsequent beats as well as the "drop-off" contour of the ventricular ejection phase in the beat immediately following point 2. In the last two beats the end of systole cannot be identified because there is no clear dicrotic incisura. It is most likely marked at the points indicated by the dotted lines in which case ventricular ejection is shortened, as logically it should be.

dilate, within limits, without suffering diminished contractile performance. It would then be the limits of myocardial distensibility or, in a sense, "compliance," to draw upon a term from pulmonary physiology, which determines the compensatory potential of the left ventricle in this disease.

MYOCARDIAL PROPERTIES AND FUNCTIONS

Rushmer* aptly pointed out some of the limitations of experimental data when applied to man, particularly regarding ventricular distensibility and contractility. Sarnoff[91] has shown that there are circumstances in which the myocardium does not behave strictly according to "Starling's law" and that the myocardial function curves vary in accordance with the state of the myocardium as affected by drugs or ischemia. Gradually the influence of the "state" of the myocardium has emerged as the explanation of what seemed to be discrepancies among some of the observations of Frank,[93] Starling,[94] Straub,[95] Wiggers,[90] and others.

In rheumatic valvular heart disease the properties of myocardial muscle assume great clinical importance since there are at least two major influences which may affect these properties. The factor of inflammatory disease has seemed the more obvious. There can be little doubt that damage to muscle resulting from infection must determine, in certain instances, the capacity of the heart to cope with valvular defects which impose abnormal demands or "compensatory" adjustments. Assuming that, in other instances, inflammatory changes are minimal, the myocardial changes resulting from factors such as hemodynamic alterations in valvular disease seems no less important.

Specifically, in mitral regurgitation the extreme degree of left ventricular dilatation which are found (Fig. 11) must by physical strain or by affecting the myocardial-capillary distribution lead to fundamental changes in elastic properties and test to the limit myocardial distensibility. The reduction of "contractile tension," demonstrated in the length-tension graph of Frank,[93] following increase in fiber length beyond a certain limit readily applies in the case of mitral regurgitation. Furthermore changes in myocardial characteristics may determine, in a manner analogous to the demonstrations of Sarnoff,[91] an entirely

* Ref. 48, chapters 6 and 7.

different type of myocardial function curve in this disease. Further differences in such a curve could parallel different stages in the evolution of this disease.

The remarkable improvement seen in the patients who have been operated at earlier stages of the disease sets a sharp contrast to the fate of those who had maximal deterioration prior to surgery. This experience, in view of and excellent long term (up to three years) results.

Correlation of Physiologic Sequelae and Life History of Patients: Consideration of the data reviewed here is conducive to certain speculations. Given a good ventricular muscle, early in mitral insufficiency, dilatation adequately maintains a compensated state. As regurgitation increases further dilatation occurs. Hemo-

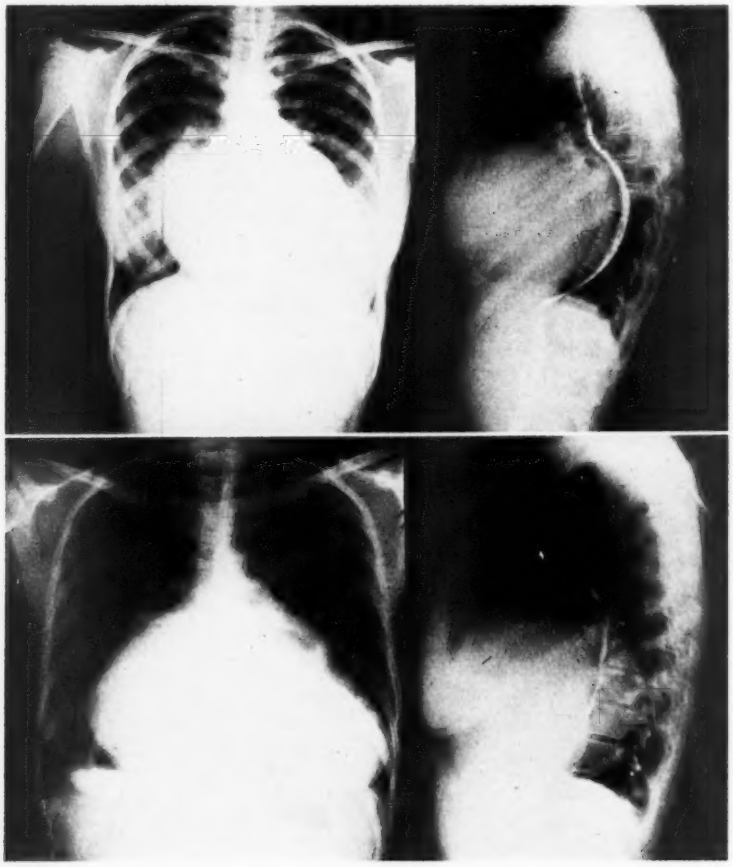

Fig. 11. An all too common finding (marked cardiac enlargement) illustrated in two cases of advanced mitral regurgitation. In these enormous hearts the elastic tolerance of the left ventricular myocardium has been exhausted.

the foregoing presentation and discussion, dictates that methods for the better selection of patients prior to the advent of irreversible myocardial damage must be developed if uniformly safe surgery and good prognosis are to be attained. Careful selection of patients, although still based on too little objective data and too much empirical impression, has nevertheless, been accompanied by decreased surgical risk

dynamic parameters which include cardiac output, pulmonary vascular pressures, left atrial pressure-pulse contour and pressures, left ventricular peak and end-diastolic pressures and peripheral pressure do not necessarily reflect the insidious changes which the myocardium is sustaining. Clinically, the patient, although at reduced efficiency, lives a comfortable and active life. This phase of the disease

will last until myocardial distensibility has been strained beyond a critical threshold. The clinical observation that rapid deterioration begins abruptly after a long course of apparent compensation suggests that the patient has reached that threshold. At some point just preceding this stage the marked changes in measurable hemodynamic phenomena become apparent.

The description of some degrees of myocardial hypertrophy in mitral insufficiency by many observers suggests that total left ventricular work may be increased at some stage of the process. Further progress, however, leads to a point at which myocardial distensibility, elasticity, or contractility are altered by overdilatation. The "engine" is now damaged. Despite increased demand or load it may be incapable of performing more work and eventually yields less than normal. The degrees of inflammatory damage sustained by the muscle may be a major determinant of the point at which the threshold of tolerance to distension is reached.

Pulmonary hypertension imposes an increased load on the right heart. When cardiac output is not significantly reduced right ventricular work must increase (hypertrophy). However, when cardiac output decreases, the work required of the right ventricle will depend upon the concomitant changes in pulmonary vascular resistance. If useful right ventricular work is increased by pulmonary vascular hypertension, it may decrease when correction of insufficiency decreases pulmonary vascular resistance significantly, assuming that changes in cardiac output do not affect this parameter in an opposite direction. But what of the patients with severe pulmonary arteriolar changes? In such instances increases in cardiac output would lead to increased load upon the right heart since pulmonary arteriolar resistance cannot be greatly decreased. A situation comparable to that which is obtained when congenital anomalies are corrected, in cases of atrial septal defect or patent ductus arteriosus with pulmonary hypertension and right-to-left shunts, can be postulated.

Cause of Surgical Failure in Advanced Cases: The experience with patients subjected to corrective surgery has been described in detail elsewhere.[26] The fact that patients in far advanced states of the disease do not appear to obtain benefit from the mechanical correction of mitral regurgitation demands an explanation. Particularly when we see completely and startlingly opposite results in what clinically appear to be less advanced cases.

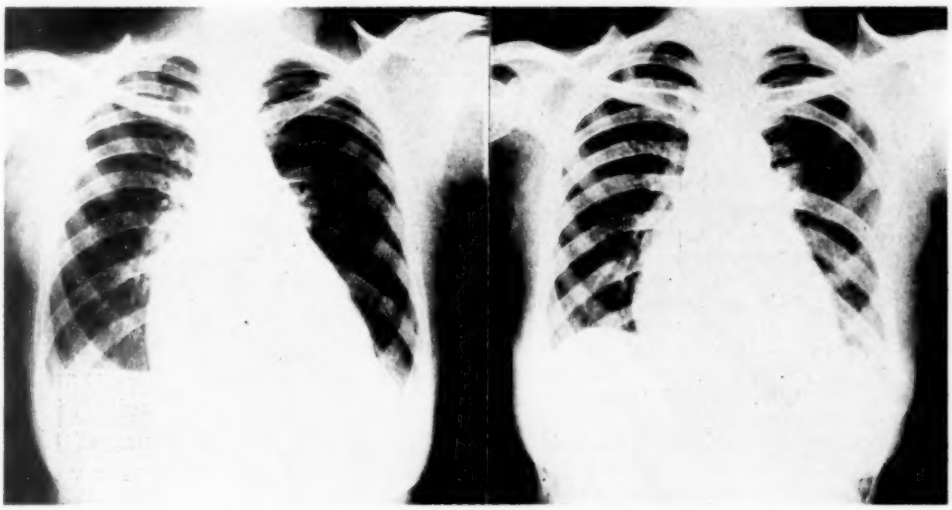

Fig. 12. X-ray appearance of a patient one week before (left) and sixteen days after (right) surgical correction of massive mitral regurgitation. Note decrease in cardiac size. In such a case stroke volume decreases, forward flow increases, and if left ventricular work increases it can be tolerated. It is in such individuals that a good prognosis may be expected following surgical treatment.

The available data support with some consistency the hypothesis that correction of mitral regurgitation, at least in the advanced cases, determines an acute increase in the work demanded of the heart. If the left ventricular myocardium is capable of meeting this demand, the patient will survive. If myocardial elasticity is satisfactory, reduction in the regurgitant flow will result in reduction of ventricular volume (Fig. 12 and 13). Shortening of myocardial fibers may affect an improvement in the characteristics of that particular myocardial function curve by a crossing back over the threshold of tolerance to distensibility. If there is no reasonable "elastic reserve" in advanced cases, the demand for greater work may not be compatible with the capabilities of the overstretched myocardium and may result in an aggravation of myocardial failure.

Ratification or correction of these observations and speculations will depend upon the development of better technics for measuring total myocardial work applicable not only in experimental animals, but also in normal and diseased man.

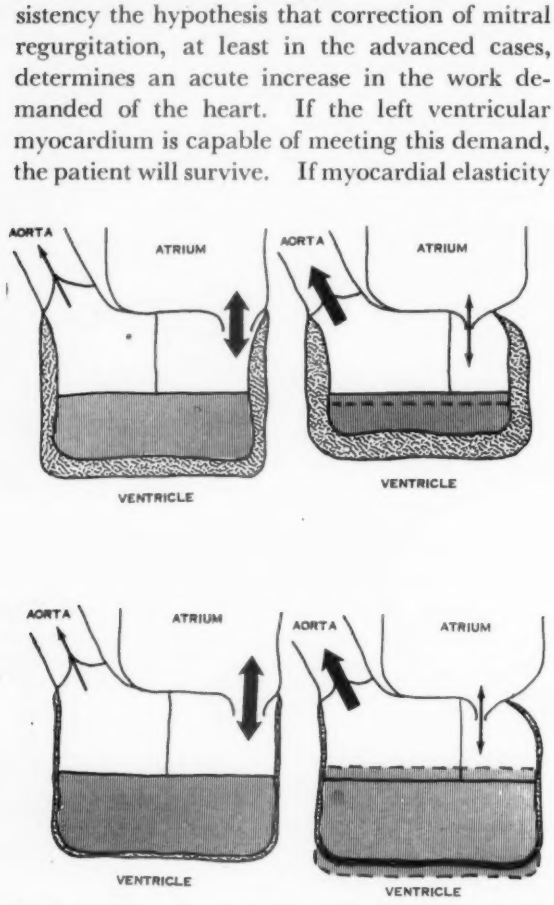

Fig. 13. The changes in left ventricular volumes are shown schematically in these diagrams. At the top is the situation which is believed to exist when mitral regurgitation is present in a heart in which the left ventricular myocardium retains elasticity or contractility. Prior to correction of the regurgitant defect (left), left ventricular stroke volume is divided into three major fractions: (1) forward volume or cardiac output, (2) residual volume, and (3) regurgitant volume. Diminution of the regurgitant defect (right) results in increased forward flow and in reduced residual volume by virtue of good muscular "tone." The changes in left ventricular work under these circumstances are not clear. This depends on the relative magnitudes of increase in forward flow, decrease in residual and regurgitant volumes, and change in total resistance to ejection. Myocardial contractile efficiency probably improves due to shortening of the overstretched fibers.

In the cases illustrated by the dye dilution curves shown in Figure 9 the situation is comparable to that illustrated here in the lower diagrams. Loss of myocardial contractility results in an increase in residual volume despite decreased regurgitation and increased forward flow. If the magnitude of these changes results in increased stroke volume, an increase in left ventricular work is determined provided that total resistances rise or do not significantly change.

Summary

A review of the characteristic changes in specific hemodynamic measurements attributable to mitral regurgitation introduces the presentation of clinical and experimental data which establish some major changes to be expected after mechanical correction of this lesion in animals and in patients.

The effects of surgical repair of mitral insufficiency are evident in a reversal of nearly all observed parameters.

The possible usefulness of analysis of transvalvular gradients as an index of the degree of regurgitation is suggested. Significant changes in the phases of the cardiac cycle and in measurements of "phasic flowgram" areas are presented and discussed with regard to their implications in explaining cardiac compensatory mechanisms in this disease.

A method for estimating ventricular volume using serially recorded dye dilution curves is presented and its deficiencies are discussed. The possible significance of these measurements in relation to myocardial work is discussed.

The significance of failure of end-diastolic pressure to fall and ventricular volume to decrease in some instances is discussed in connection with the elastic properties of the ventricular myocardium.

The following conclusions are suggested:

(1) Mechanical correction of mitral re-

gurgitation reverses nearly all the known changes in hemodynamic parameters.

(2) The major compensatory factor in mitral insufficiency is left ventricular dilatation. Improved ventricular contraction by virtue of dilatation seems unlikely. Ability of the myocardium to continue to function depends on its tolerance to distension without decrease in contractility.

(3) Mitral regurgitation results in a decrease of the useful work of the heart in the late stage of the disease.

(4) When overdilatation has gone beyond certain limits, dependent on inflammatory or mechanical damage to myocardial tissue, correction of the valvular lesion may aggravate the myocardial dysfunction by imposing an increased work load on the muscle.

(5) The evidence presented suggests that only by the selection of surgical candidates prior to the onset of irreversible (myocardial overdilatation) stages will lasting benefit be obtained from surgical corrective measures.

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Evidence for Retrograde Transpulmonary Propagation of the V (or Regurgitant) Wave in Mitral Insufficiency*

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A NUMBER of investigators have reported the occurrence of a prominent V (or regurgitant) wave in the wedged pulmonary artery tracing when a significant degree of mitral insufficiency is present. These workers have even distinguished between mitral stenosis and mitral insufficiency on the basis of this observation.[1–5] Although this view has not been universally accepted,[6,7] there is considerable evidence in the literature which supports this concept.[8–10] The authors have observed seven cases of mitral insufficiency with giant V waves in the wedged position and, in addition, an unusually prominent wave in the right and main pulmonary arteries. The purpose of this paper is to present hemodynamic studies of these seven cases and to offer a possible explanation of the unusual findings.

METHODS

The patients used in this study were prepared for cardiac catheterization in the conventional manner. Simultaneous records of pressures from the catheter and the electrocardiogram were obtained. The pressure recording system consisted of a Sanborn direct writing Visocardiette† and Statham type P-23A pressure transducers.‡ Pressure curves were recorded from a wedged position in the peripheral pulmonary artery, the right pulmonary artery, and from the main pulmonary artery. The wedged pulse pressure contours were correlated with the findings from both the right and main pulmonary arteries. Mean pressures were calculated by means of a planimeter. Pulmonary arteriolar resistance was calculated according to the method of Gorlin *et al.*[11] Oxygen consumption was obtained by collecting samples of expired air in Douglas bags and subsequent Haldane analysis. Cardiac output was determined by the direct Fick technic utilizing manometric Van Slyke blood gas analysis.

RESULTS AND CASE HISTORIES

CASE 1. A 54-year-old white male was admitted on July 12, 1957 for cardiac catheterization. A heart murmur had first been noted around the age of 10 years. At the time of hospital entry, the only complaint was slight fatigue after moderate exertion.

Physical examination revealed the following cardiovascular findings: The blood pressure was 112/72 mm Hg. The peripheral pulses were all palpable. The lungs were clear to percussion and auscultation. Grade I cardiac enlargement was present, the point of maximum impulse and the apex beat being in the 5th intercostal space 1 cm lateral to the midclavicular line. There was a systolic thrill at the apex. The rhythm was regular, the rate, 76 per minute. A grade IV pansystolic murmur, which obliterated the first sound, was present at the apex. The murmur was transmitted to the axilla and also to the left sternal border and the base of the

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‡ Statham Laboratories, Inc., Los Angeles, California.

heart. The pulmonary 2nd sound was split and greater than the aortic 2nd sound. There was a low-pitched diastolic filling sound present over the nipple area.

The electrocardiogram was normal. Roentgenographic examination of the chest showed grade I cardiac enlargement, with slight posterior prominence of the left ventricle on the oblique view. There was no left atrial enlargement by x-ray. The clinical diagnosis was probable rheumatic heart disease with mitral insufficiency.

Data collected at cardiac catheterization are shown in Table I.

tour from the wedged position in the right pulmonary artery (Fig. 1A). The mean pressure here is 13 mm Hg. As the catheter is withdrawn into the right pulmonary artery, the V wave is again visible on the right border of the systolic ejection wave. This occurs at approximately the same time in the cardiac cycle as the V wave in the wedged position. The height of the V wave in the right pulmonary artery is approximately equal to the systolic ejection pressure (Fig. 1B). The right pulmonary artery pressure is 25/9 mm Hg, and the mean pressure is 17 mm Hg. As the catheter is

TABLE I

Hemodynamic Findings at Cardiac Catheterization

Case no.	Valve lesion	Pressures (mm Hg)								Pulmonary arteriolar resistance, dyne sec cm^{-5}	Cardiac output, *l*/min	Cardiac index, *l*/min/M^2/BSA
		RA S/D	RV S/D	MPA S/D	MPA Mean	RPA S/D	RPA Mean	PPA S/D	PPA Mean			
1.	M.I.	4/0	27/−3	25/7	17	25/9	17	29/7	13	61	5.2	2.7
2.	M.I., A.I., A.S.	7/0	42/5	42/21	35	*	*	42/19	25	199	4.0	3.1
3.	M.I.	3/1	26/2	26/10	18	25/14	16	27/14	18	0	6.6	3.0
4.	M.I., A.I.	8/0	55/10	50/25	38	65/25	36	65/25	33	22	1.8	1.1
5.	M.I., A.I.	3/1	23/5	23/10	14	*	*	28/13	16	46	3.4	1.8
6.	M.I.	7/4	36/4	36/15	19	*	*	30/15	18	63	1.5	.8
7.	M.I., M.S.	10/6	56/4	52/32	41	56/30	39	53/25	35	71	6.8	3.8

* Not measured.

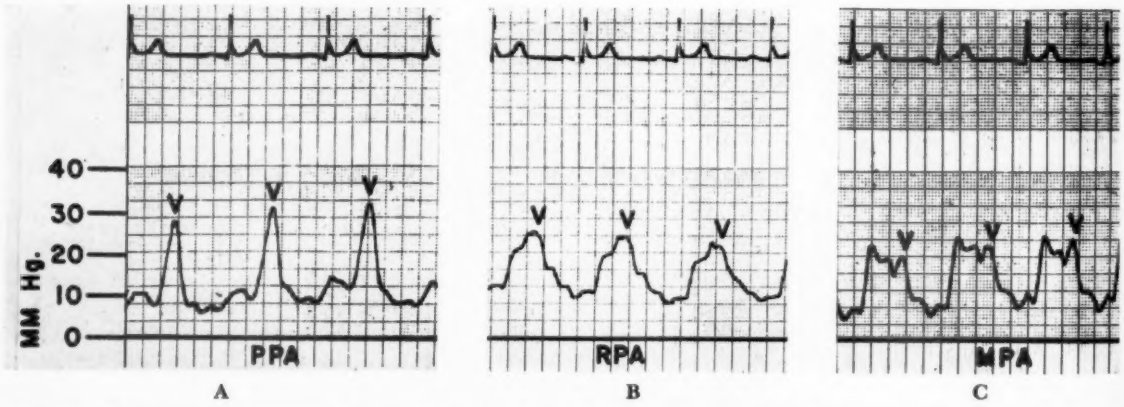


Fig. 1A. Pulse pressure contour in the right peripheral pulmonary artery (wedged position). (B) Pulse pressure contour in the right pulmonary artery. (C) Pulse pressure contour in the main pulmonary artery.

Pressure tracings obtained from the right peripheral pulmonary artery, the right pulmonary artery, and the main pulmonary artery are shown in Fig. 1A, 1B, 1C, respectively. A very prominent V wave with pressure amplitude of 29/7 mm Hg is noted in the pressure con-

further withdrawn into the main pulmonary artery, the V wave is displaced to the right and is somewhat lower down on the descending limb of the pulmonary artery pressure curve (Fig. 1C). The pressure here is 25/7 mm Hg, and the mean pressure is 17 mm Hg. It is

to be noted that the systolic peak in the wedged position occurs at approximately the same time as the V wave in the main pulmonary artery.

CASE 2. This 48-year-old white woman was admitted on January 30, 1957 for cardiac catheterization. As a child she had rheumatic fever, and at the age of 40 years she was found to have heart murmurs. She had increasing exertional dyspnea for several years prior to her hospital entry and a number of bouts of palpitation. Physical examination showed the following cardiovascular findings: The blood pressure in the arms was 144/76 mm Hg. The peripheral pulses were all palpable. The lungs were clear to percussion and auscultation. The point of maximum impulse and the apex beat were in the 5th intercostal space 1 cm lateral to the midclavicular line. There was a soft systolic thrill at the apex. The rhythm was regular and the rate was 82 per minute. The 2nd pulmonary sound was accentuated. There was a grade II blowing pansystolic murmur heard at the apex and well transmitted to the axilla. There was a grade II relatively harsh systolic murmur heard over the aortic area. There was a grade III blowing pandiastolic murmur heard along the left sternal border.

The electrocardiogram was normal. Roentgenographic examination of the chest showed rounding of the left ventricle and encroachment upon the retrocardiac space in the left anterior oblique position consistent with left ventricular hypertrophy. In the posteroanterior view a double density and elevation of the left main bronchus were visible, indicating left auricular enlargement. Clinical diagnosis was rheumatic heart disease, mitral insufficiency, aortic stenosis and aortic insufficiency.

Findings obtained at cardiac catheterization are given in Table I. Figures 2A and 2B give the pressure tracings obtained from the right peripheral pulmonary artery, main pulmonary artery and right ventricle, respectively. Pressure recordings from the wedged position in the right pulmonary artery show a very prominent V wave (Fig. 2A). The pressure here is 42/19 mm Hg, and the mean pressure is 25 mm Hg. In the main pulmonary artery, a prominent V wave is again visible on the right of the systolic ejection curve exceeding the peak of the systolic ejection curve by 1–3 mm Hg. The peak of the V wave is 42 mm Hg in both the wedged position and the main pulmonary artery (Fig. 2B). The pressure in the main pulmonary artery is 42/21 mm Hg, with a mean pressure of 35 mm Hg. Thus, the mean pressure in the main pulmonary artery is greater than that in the peripheral pulmonary artery.

CASE 3. A 17-year-old white male was admitted on March 2, 1956 for cardiac catheterization. At age 13 years he first noticed attacks of palpitation and weakness. Examination by a local physician revealed a heart murmur. At the present time the only complaints are occasional attacks of palpitation.

Physical examination revealed the following cardiovascular findings: The blood pressure in the arms was 138/60 mm Hg. The peripheral pulses were all palpable and had a mild collapsing quality. A pigeon breast deformity of the chest was present. The lungs were clear to percussion and auscultation. Grade I cardiac enlargement was present, the point of maximum impulse and the apex beat being in the 6th interspace at the midclavicular line. A prominent systolic thrill and a left ventricular lift were palpable at the apex. The rhythm was regular, the rate, 68 per minute. A grade IV harsh pansystolic murmur which obliterated both the 1st and 2nd heart sounds was present at the apex. The murmur was transmitted to the axilla and the angle of the left scapula and also to the left sternal border as well as to the base of the heart. The pulmonary second sound was split and greater than the aortic 2nd sound.

Electrocardiographic studies revealed right axis

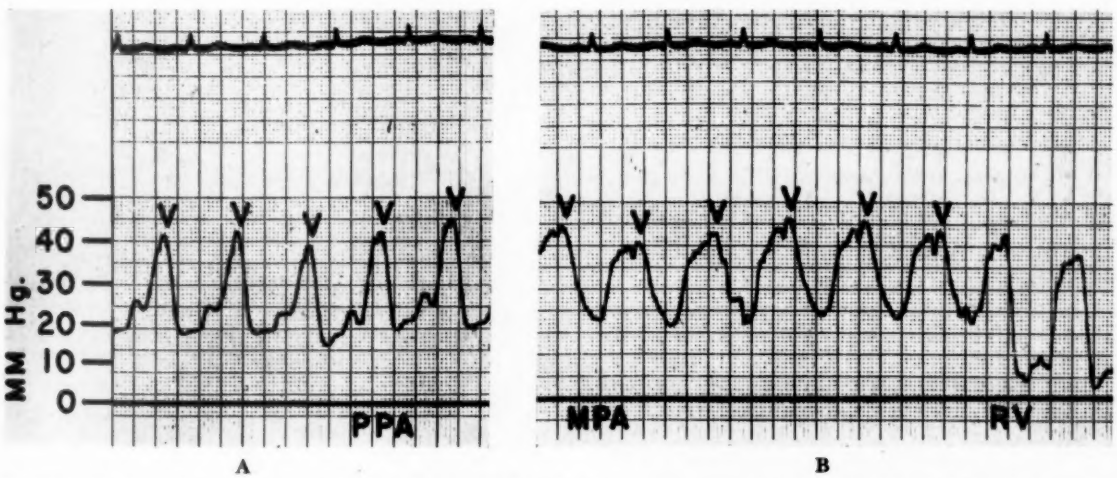


Fig. 2A. Pulse pressure contour in the right peripheral pulmonary artery (wedged position). (B) Pulse pressure contour in the main pulmonary artery and right ventricle.

deviation and the interpretation was that of a vertical heart. Roentgenographic examination of the chest showed borderline enlargement of the left ventricle in the posteroanterior view, and grade I enlargement of the left atrium in the right anterior oblique view. The clinical diagnosis was rheumatic heart disease with mitral insufficiency.

Findings obtained at cardiac catheterization are given in Table I. Figures 3A, 3B, and 3C give the pressure tracings obtained from the wedged pulmonary artery, 25/14 mm Hg, and the mean pressure is 16 mm Hg. As the catheter is further withdrawn into the main pulmonary artery, the peak of the V wave appears to be further displaced to the right and lower down on the descending limb of the pulmonary artery pressure curve (Fig. 3C). The pressure here is 27/11 mm Hg, and the mean pressure is 18 mm Hg. It is to be noted that the systolic peak in the wedged position (27 mm Hg) is approximately the same as that in the main pulmonary artery (26 mm Hg).

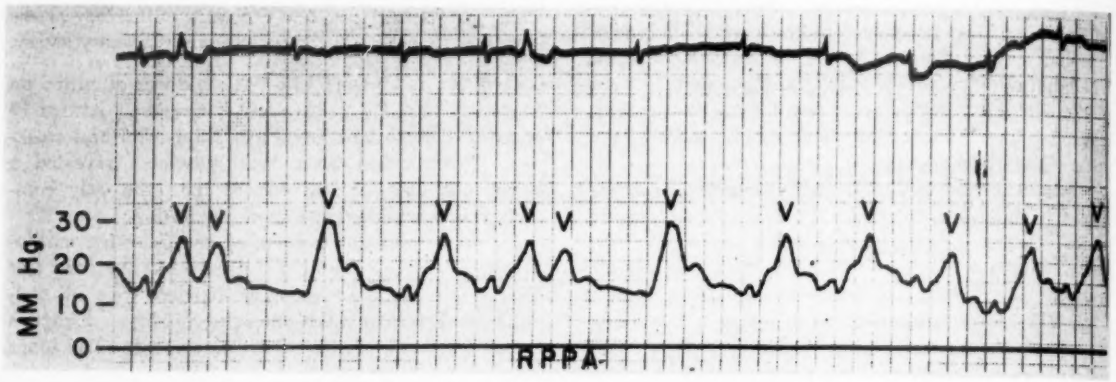
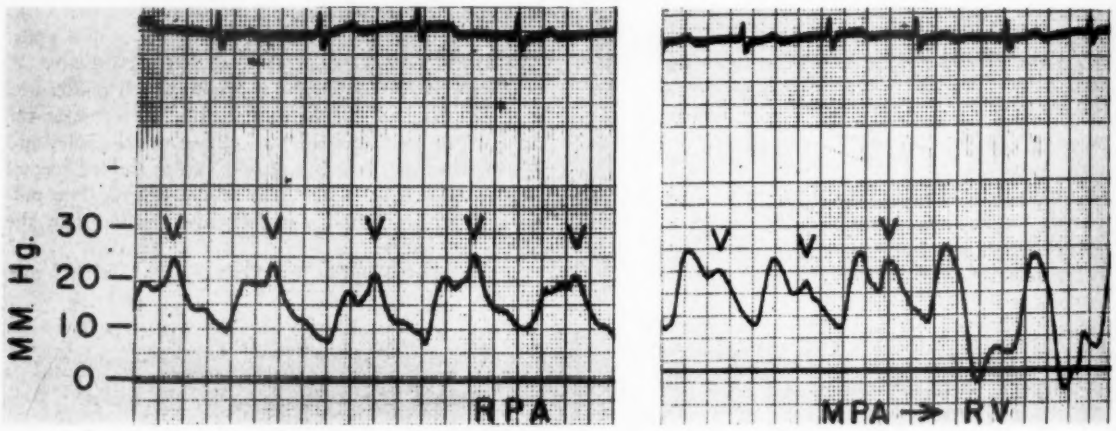


Fig. 3A. Pulse pressure contour in the right peripheral pulmonary artery (wedged position).



B C

Fig. 3B. Pulse pressure contour in the right pulmonary artery. (C) Pulse pressure contour as the catheter is passed from main pulmonary artery to right ventricle.

the right pulmonary artery, and the main pulmonary artery, respectively. A very prominent V wave with pressure amplitude of 27/14 mm Hg is noted in the pressure contour from the wedged position in the pulmonary artery (Fig. 3A). The mean pressure here is 18 mm Hg. As the catheter is withdrawn into the right pulmonary artery, a large V wave is visible (Fig. 3B). This occurs at approximately the same time of the cardiac cycle as the V wave in the wedged position and its peak pressure exceeds the systolic ejection pressure by approximately 5 to 6 mm Hg. The right pulmonary artery pressure is

Case 4. A 48-year-old white female was admitted on July 21, 1955 for cardiac catheterization. She had been told of a heart murmur at the age of 19 years, and at 39 years of age had subacute bacterial endocarditis for which she received intensive pencillin therapy. On the present admission to the hospital, the patient complained of shortness of breath on climbing one-half flight of stairs, and even the mildest exertion was followed by fatigue. Because of this her activity had been restricted. She had no history of having had congestive heart failure or of having received digitalis preparations.

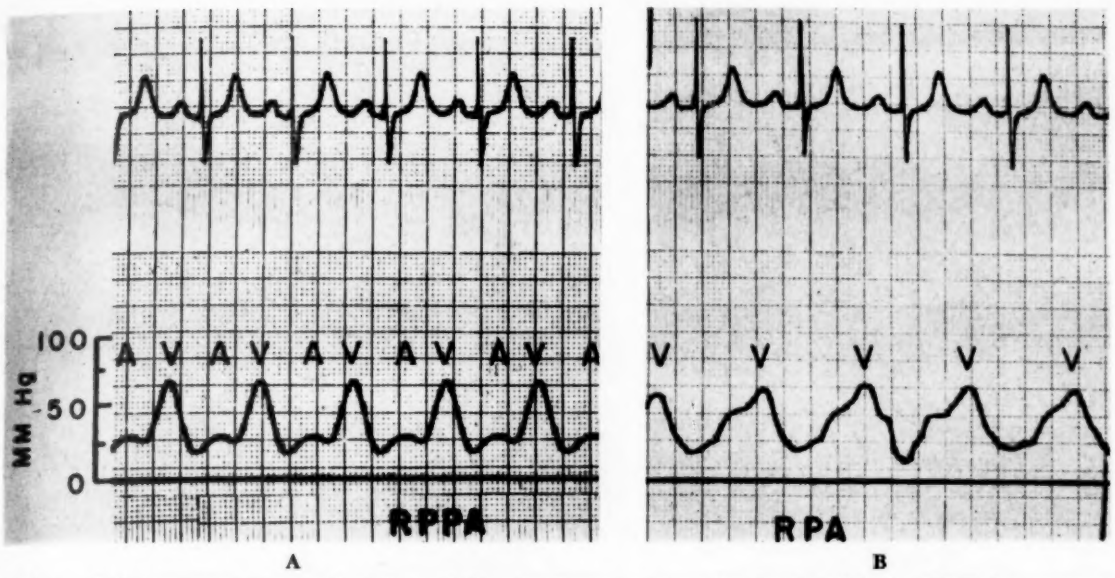


Fig. 4A. Pulse pressure contour in right peripheral pulmonary artery (wedged position). (B) Pulse pressure contour in right pulmonary artery near hilus of right lung.

Physical examination revealed the following cardiovascular findings: The blood pressure in the arms was 158/60 mm Hg. The peripheral pulses were all palpable and had a collapsing quality. The lungs were clear to percussion and auscultation. Grade II cardiac enlargement was present, the point of maximum impulse and apex beat being in the 5th intercostal space at the anterior axillary line. A prominent systolic thrill was palpable at the apex. The rhythm was regular, the rate, 78 per minute. The 1st and 2nd heart sounds at the apex were obscured by a grade IV pansystolic murmur, which was transmitted to the axilla and heard well posteriorly at the angle of the left scapula. The murmur also radiated to the left border of the sternum in the 2nd, 3rd, and 4th left interspaces. The murmur decreased with deep inspiration. The pulmonary 2nd sound was present and the aortic 2nd sound inaudible. There was a grade IV, high-pitched, early, blowing diastolic murmur best heard along the left sternal border in the 3rd and 4th interspaces.

Electrocardiographic studies revealed left axis deviation and slight prolongation of the P-R interval. Roentgenographic examination of the chest showed grade II enlargement of the left ventricle in the posteroanterior view and grade II enlargement of the left atrium in the right anterior oblique view. Collapsing pulsation of the aorta was observed at fluoroscopy. The clinical diagnosis was rheumatic heart disease with mitral insufficiency and aortic insufficiency.

Findings obtained at cardiac catheterization are given in Table I. Figures 4A, 4B, and 4C give the pressure tracings obtained from the wedged pulmonary artery, the right pulmonary artery, the main pulmonary artery, and right ventricle, respectively. A very prominent V wave is noted in the pressure record from the wedged position in the pulmonary artery (Fig. 4A). The pressure here is 65/25 mm Hg, and the mean pressure is 33 mm Hg. In the right pulmonary artery (Fig. 4B), a prominent V wave is visible and appears upon the descending limb of the pulse pressure curve. The peak of the V wave in the right pulmonary artery is equal to that of the V wave in the wedged position (65 mm Hg). The pressure in the right pulmonary artery is 65/25 mm Hg, and the mean pressure is 36 mm Hg. In the main pulmonary artery (Fig. 4C), an "M" shaped configuration of the pulse pressure curve is observed; the second peak occurring in diastole equals the systolic ejection pressure. The pressure in the main pulmonary artery is 50/25 mm Hg, and the mean pressure is 38 mm Hg. It is unusual to find the systolic pressure in the wedged position higher than in the main pulmonary artery, as observed here. However, the mean pressure is higher in the main pulmonary artery than in the wedged position. Thus, a functional pressure gradient for the pulmonary circulation is present.

Case 5. A 27-year-old white male was admitted on January 27, 1956 for cardiac catheterization. He had a history of rheumatic fever at the age of 16 years. At age 22 he had subacute bacterial endocarditis treated by intensive penicillin therapy. During the past year he had two episodes of paroxysmal nocturnal dyspnea.

Physical examination revealed the following cardiovascular findings: The blood pressure in the arms was 140/40 mm Hg. Peripheral pulses were all palpable and had a marked collapsing quality. A palpable systolic thrill was present over both external carotids. The lungs were clear to percussion and auscultation. The heart was enlarged to grade II, the point of maximum impulse and apex beat being in the 5th interspace 2 cm to the left of the midclavicular line. The rhythm

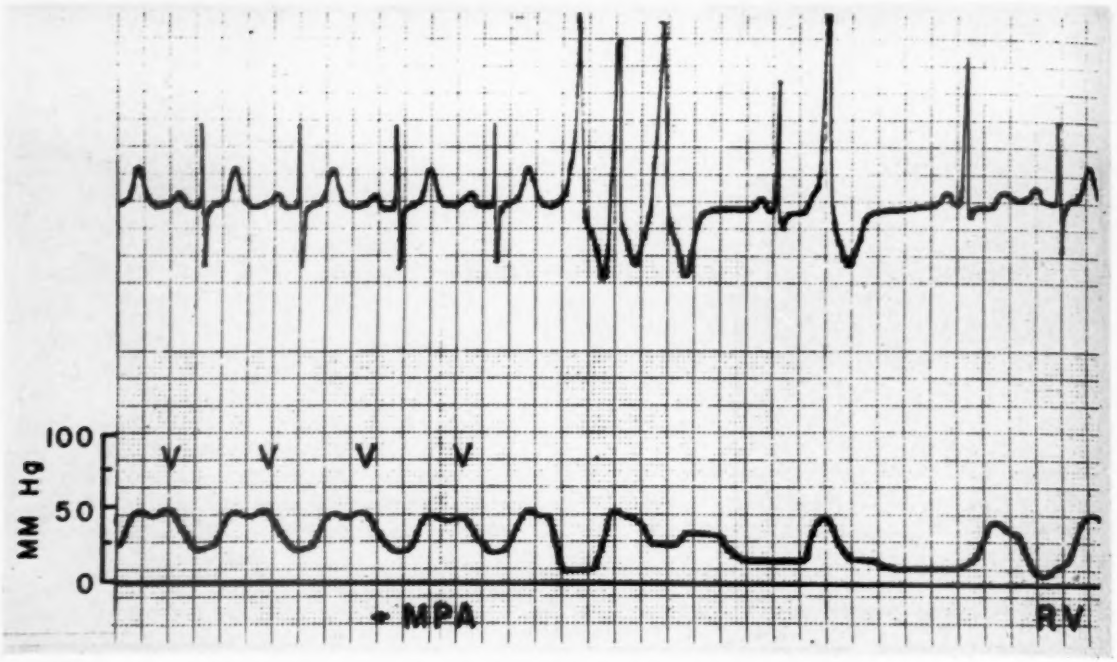


Fig. 4C. Pulse pressure contour as catheter passed from main pulmonary artery to right ventricle.

was grossly irregular. The apical rate was 65, and there was no pulse deficit. A palpable systolic thrill was present at the apex. At the apex the 1st heart sound was replaced by a grade IV pansystolic murmur, which was transmitted to the axilla and to the angle of the left scapula. This murmur was also transmitted toward the left sternal border. A 3rd heart sound was present at the apex. At the 3rd and 4th interspaces just to the left of the sternum, there was a grade IV, high-pitched whining, musical diastolic murmur which was transmitted down toward the apex. At the 2nd interspace just to the right of the sternum, there was a harsh grade II systolic murmur transmitted into the neck.

Electrocardiographic findings revealed auricular fibrillation and left ventricular hypertrophy. Roentgenographic examination of the chest showed generalized grade III cardiac enlargement in the posteroanterior view and grade II enlargement of the left atrium in the right anterior oblique view. In the left anterior oblique view, there was grade II to grade III enlargement in the region of both the right and left ventricles. Collapsing pulsations of the aorta were observed at fluoroscopy. The clinical diagnosis was rheumatic heart disease with mitral insufficiency, aortic insufficiency, and mild aortic stenosis.

Data obtained at cardiac catheterization are shown in Table I. Pressure tracings obtained from the right peripheral pulmonary artery and the main pulmonary artery are shown in Figures 5A and 5B, respectively. The pressure in the wedged position (Fig. 5A) in the peripheral pulmonary artery is 28/13 mm Hg, and the mean pressure is 16 mm Hg. A prominent V wave is visible (Fig. 5B) and appears on the descending limb of the main pulmonary artery pulse pressure contour. This wave again approximates the peak of the systolic ejection. The pressure in the main pulmonary artery is 23/10 mm Hg, and the mean pressure is 14 mm Hg. It is to be noted that the peak of the V wave in the wedged position is 5 mm higher than the peak systolic pressure in the main pulmonary artery. The pulse pressure contour in the main pulmonary artery again shows an "M" shaped configuration, with the first peak of the "M" being the systolic ejection pressure and the second peak, the V wave. The mean pressure in the peripheral pulmonary artery is 16 mm Hg, while the mean pressure in the main pulmonary artery is 14 mm Hg. In this instance, the mean pressure is slightly higher in the wedged position than in the main pulmonary artery. However, these figures are not significantly different when one considers the overall accuracy of this measurement. Also, the fact that these two pressures were not recorded simultaneously is of significance.

Case 6. A 30-year-old white male was admitted on June 18, 1956 for cardiac catheterization. Between the ages of 10 and 21 years, he had four episodes of rheumatic fever. At 17 years of age he first noticed dyspnea on exertion. In spite of this he served on active duty for three years in the U. S. Navy. Subsequent to this he noted an increase in exertional dyspnea. At 27 years of age he had a mitral valvulotomy. One month after surgery he had a recurrence of rheumatic fever. On admission he claimed that he had not been

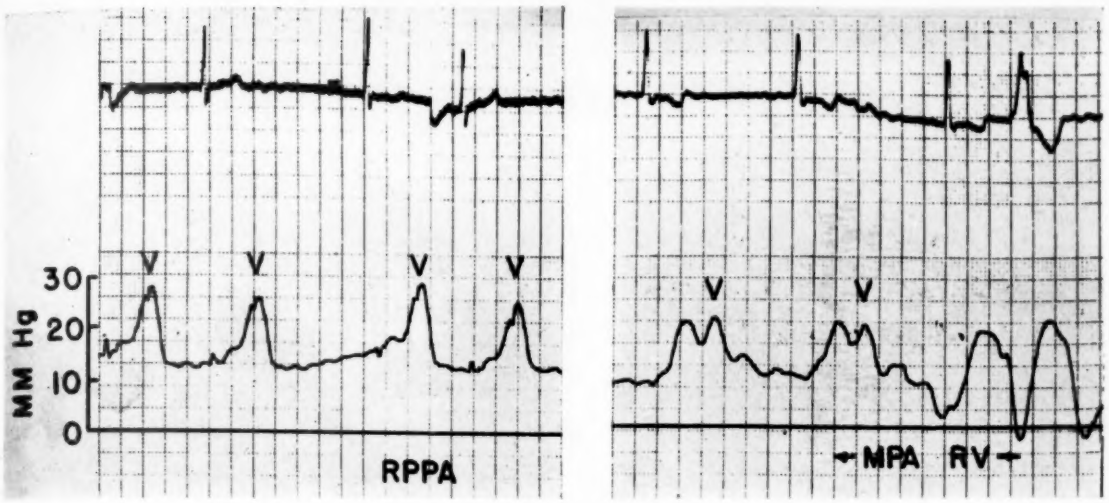


Fig. 5A. Pulse pressure contour in the right peripheral pulmonary artery (wedged position). (B) Pulse pressure contour as catheter passed from main pulmonary artery to right ventricle.

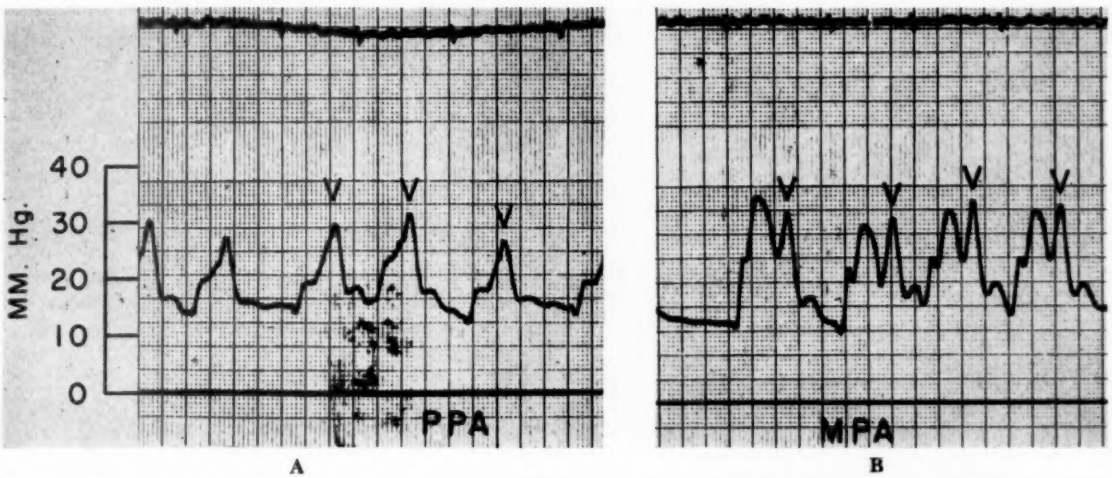


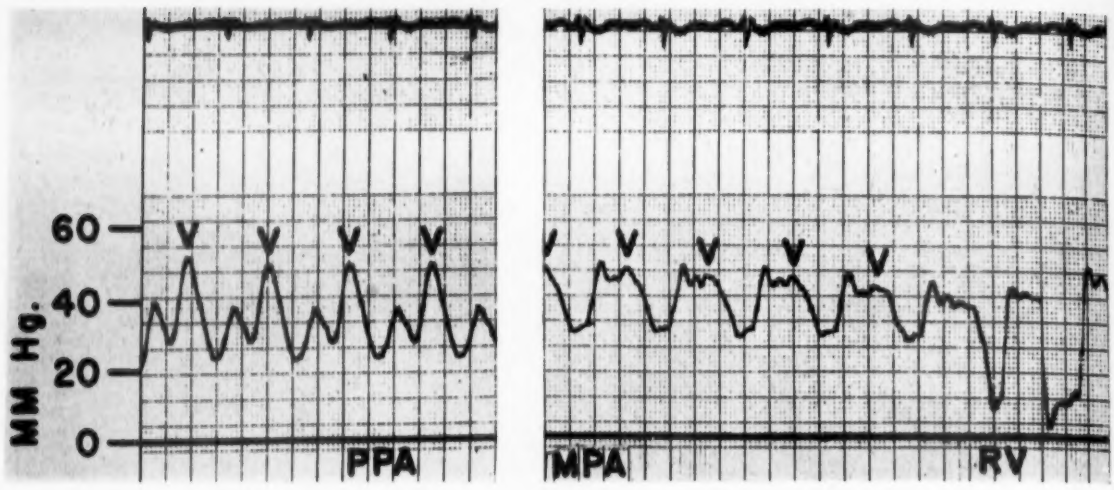
Fig. 6A. Pulse pressure in the right peripheral pulmonary artery (wedged position). (B) Pulse pressure contour in the main pulmonary artery.

benefited by the surgery and was unable to walk one-half block without experiencing dyspnea.

Physical examination revealed the following cardiovascular findings: The blood pressure in the arms was 122/66 mm Hg. The lungs were clear to percussion and auscultation. The heart was enlarged grade II to III, the point of maximum impulse being in the 6th intercostal space 2 cm to the left of the midclavicular line. The rhythm was irregular due to auricular fibrillation. The apical rate was 68, without pulse deficit. A 3rd diastolic heart sound and a grade III pansystolic murmur were heard at the apex.

Electrocardiograms revealed auricular fibrillation and left ventricular hypertrophy. Roentgenographic examination of chest showed grade II cardiac enlargement. In the right anterior oblique view there was grade II enlargement of the left atrium, and in the left anterior oblique view there was grade II enlargement of the left ventricle. The clinical diagnosis was rheumatic heart disease with mitral insufficiency, post commissurotomy for mitral stenosis.

Data obtained at cardiac catheterization are summarized in Table I. Pressure tracings obtained from the right peripheral pulmonary artery and the main pulmonary artery are shown in Figures 6A and 6B, respectively. The pressure in the wedged position (Fig. 6A) is 30/15 mm Hg, and the mean pressure is 16 mm Hg. A prominent V wave is visible (Fig. 6B) and appears on the descending limb of the main pulmonary artery pulse pressure contour. The peak of this wave closely



A B

Fig. 7A. Pulse pressure contour in the right peripheral pulmonary artery (wedged position). (B) Pulse pressure contour in the main pulmonary artery.

approximates the peak of the V wave in the wedged position (Fig. 6A). The pressure in the main pulmonary artery is 36/15 mm Hg, and the mean pressure is 19 mm Hg. The pressure contour in the main pulmonary artery shows an "M" shaped configuration, the first peak of the "M" representing the systolic ejection peak and the second peak a V wave that at times equals or exceeds the peak of systolic ejection. The mean pressure in the peripheral pulmonary artery is 18 mm Hg, while in the main pulmonary artery the mean pressure is 19 mm Hg. These two mean pressures are not significantly different.

Case 7. A 36-year-old white woman was admitted on March 25, 1957 for cardiac catheterization. She gave a history of increasing dyspnea over the preceding five years. In the two months preceding her hospital entry she had several episodes of paroxysmal nocturnal dyspnea. She developed edema, but this cleared with digitalis therapy.

Physical examination revealed the following cardiovascular findings: The blood pressure in the arms was 132/68 mm Hg. The peripheral pulses were all palpable. The lungs were clear to percussion and auscultation. The heart was enlarged, with the point of maximum impulse and the apex beat being in the 6th intercostal space, 3 cm lateral to the midclavicular line. A systolic thrill was felt at the apex. The rhythm was regular and the rate was 82 per minute. There was a short, low-pitched mid-diastolic filling sound at the nipple area. There was a grade III blowing pansystolic murmur at the apex which largely replaced the 1st sound. This murmur was well transmitted to the axilla. There was also a short rough grade II presystolic murmur at the apex.

Electrocardiographic studies revealed incomplete left bundle branch block and digitalis effect. Roentgenographic examination of the chest revealed grade III cardiac enlargement. There was a double density in the posteroanterior view indicating left atrial enlargement. Grade I left atrial enlargement and grade II left ventricular enlargement were present. In the left anterior oblique view there was enlargement of the left ventricle. The clinical diagnosis was rheumatic heart disease with mitral insufficiency and mitral stenosis.

Data obtained at cardiac catheterization are shown in Table I. Pressures obtained from the right peripheral pulmonary artery and the main pulmonary artery are shown in Figures 7A and 7B, respectively. A prominent V wave is present in the wedged position of the right pulmonary artery (Fig. 7A). The pressure here is 53/25 mm Hg, and the mean pressure is 35 mm Hg. In the main pulmonary artery pressure tracing the prominent V wave is noted to be as high as the systolic ejection wave, giving rise to an "M" shaped wave (Fig. 7B). The pressure here is 52/32 mm Hg, and the mean pressure is 41 mm Hg.

Discussion

Close inspection of the pulse pressure contours in the wedged and main pulmonary artery permits the following observations. First, the peak pressure of the wedged V waves closely approximated the peak of systolic ejection in the main pulmonary artery. Secondly, the large V waves noted in the main pulmonary artery also had a pressure peak approximating that of V wave in the wedged position. This V wave occurred at approximately the same time in both of these stations. Finally, in the main pulmonary artery pulse pressure contour the peak of the V wave

approximated the peak of the systolic ejection wave.

In the main pulmonary artery the dicrotic wave is usually due to closure of the pulmonic valve. The height of the V wave in the cases presented was higher than that which occurs with a dicrotic wave and, in fact, in several of the cases it equalled or exceeded the peak of systolic ejection.

MacCollum and McClure[12] in 1906 produced mitral insufficiency in dogs. These investigators proved that the regurgitant wave of mitral insufficiency was transmitted retrograde from the left atrium through the pulmonary capillary bed arriving finally in the pulmonary artery. Abnormal pulmonary artery pulse pressure contours in mitral insufficiency have also recently been described by Radner.[13]

The diagnosis of mitral insufficiency in these cases is based on clinical data. In three patients the clinical impression was isolated mitral insufficiency. Although it is recognized that the absence of a diastolic murmur at the apex does not exclude mitral stenosis, it was our opinion that in three of the cases mitral insufficiency alone was present. Of the remaining four cases one had combined mitral stenosis and insufficiency (case 7). It is recognized that there is a possibility that the contour of the pressure pattern was considerably modified by the mitral stenosis. In the final three cases mitral insufficiency was associated with aortic stenosis and insufficiency, in two instances, and with aortic insufficiency in one.

The authors agree with other investigators in this field that the height of the regurgitant "V" wave bears no direct relationship with either the degree of mitral insufficiency or the amount of left atrial enlargement. It was noted that marked left atrial enlargement did not occur in any of these cases. In fact, the left atrium was observed to be zero to grade II enlarged.

Of considerable interest in all seven of these cases was the fact that oxygenated blood pulsated out of the catheter when it was in the wedged pulmonary artery position. This pulsation of blood from the catheter in the wedged position has not been observed in other cases.

Two conditions are present in the cases studied which favor the retrograde transmission of the V (or regurgitant) wave of mitral insufficiency from the left atrium through the pulmonary veins, capillaries, arterioles, and to the main pulmonary artery. These are (1) an increase in tone of the vessels of the pulmonary tree, and (2) little or no change in the normally low pulmonary vascular resistance.

Increased Tone of Pulmonary Vessels: The V wave described here originates in the left atrium. Without an increase in the tone of the wall of the pulmonary veins, it is unlikely that the wave would be transmitted. Consider the fact that the systolic ejection peak of the pulmonary artery is transmitted through the pulmonary capillaries into the pulmonary venules. Evidence for this is seen in those cases where it is possible to obtain a wedged pulmonary vein pressure tracing. Figure 8 is an example of such a case. In this instance, the catheter was passed through an atrial septal defect and wedged in a pulmonary vein. Similar data has been reported by Wilson *et al.*[14] and Connolly and Wood.[15] As also can be seen by Figure 8, tracings from the free pulmonary vein failed to show the systolic ejection peak from the pulmonary arterial system. It has been completely damped out by the elasticity of the venous tree. The wedged pulmonary artery pressure in this case was normal.

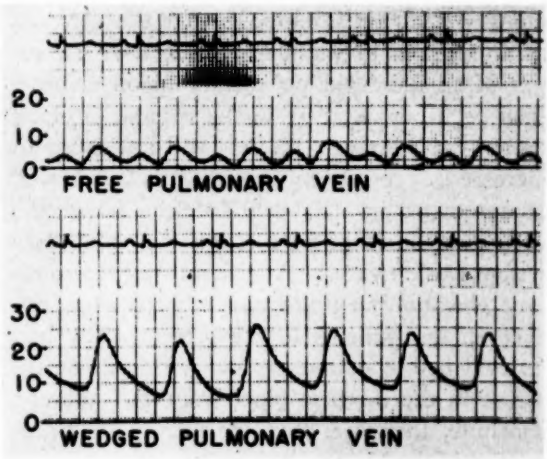


Fig. 8. Pulse pressure contours in the wedged pulmonary vein and in the free pulmonary vein recorded from a patient with atrial septal defect.

Pulmonary vascular pressure measurements usually reflect changes in the tone of the pul-

monary vascular bed. The mean pressures in all of the segments of the pulmonary arterial tree were found to be elevated in the cases of mitral insufficiency presented in this paper. These increased pressures resulted from the fact that the V waves were superimposed on the descending limb of the pulmonary arterial pressure curve. The duration and magnitude of the observed V waves are sufficient to account for the observed increase in mean pressures. Also, it was noted that the systolic peak of the V wave in the wedged position was equal to or exceeded the systolic peak of the main pulmonary artery pressure.

Further, the mean pressure in the pulmonary venous system was also elevated as evidenced by wedged pulmonary artery pressure measurements. This increase in mean pressure in the pulmonary vascular tree is evidence that there is in fact an increased vascular tone in the pulmonary bed. It is unlikely that the elevated mean pulmonary vascular pressures are the result of an increased pulmonary blood volume. First of all, an increase in the volume of blood within the pulmonary system will not cause an increase in pressure by itself. This fact is well demonstrated in atrial septal defects where the volume of blood going through the pulmonary system can be very high without any concomitant elevation in pulmonary venous pressures. Second, the patients in the present study had no evidence of pulmonary congestion or an increase in the thoracic blood volume. We can conclude, therefore, that the retrograde transmission of the V wave is due, in part at least, to an increase in the tone of the pulmonary vascular bed.

Normal Pulmonary Vascular Resistance: The second requisite for retrograde transmission of the V wave, namely that of a normal pulmonary vascular resistance, has been observed in these seven patients with mitral insufficiency. Calculation of their pulmonary arteriolar resistance gave normal or reduced values, indicating no significant change in pulmonary vascular resistance.

The pulmonary vascular bed can change its vascular capacity so that it functions as a blood reservoir for the body as a whole.[16] These changes in capacity are brought about by means of the autonomic control of this bed. The normal pulmonary arterioles are, however, short, and the media has a scanty amount of smooth muscle, as compared to their counterparts in the systemic circulation. Thus, changes in the tone of the normal pulmonary vessels are not accompanied by demonstrable changes in the overall pulmonary vascular resistance. In the cases presented here, an increase in the tension of the walls of the veins greatly facilitates the retrograde transmission of the V wave. An increase in resistance at the level of the pulmonary arterioles would act in an opposite manner. It has been shown, however, that in these seven patients with mitral insufficiency there was no increase in the pulmonary arteriolar resistance.

Summary

(1) Seven patients with mitral insufficiency and giant V waves in the wedged pulmonary artery position have been studied.

(2) The systolic peak of the V (or regurgitant) wave approximated the systolic peak of the right and main pulmonary artery pressure curves.

(3) Pulmonary arteriolar resistance was found to be normal or reduced.

(4) A consideration of the hemodynamic data favors the concept that in mitral insufficiency a retrograde transmission of the V wave may occur and that it results from an increase in the tone of the pulmonary vascular system without an increase in the pulmonary vascular resistance.

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Clinical Studies

Heart Size in Adolescents*

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THIS report deals with measurements of the heart obtained from the teleoroentgenograms of 2,138 healthy school children, aged 12 through 17 years. It contains a table of "standard values" based on an analysis of these measurements. Some of these values differ significantly from those of other investigators whether presented as tables, nomograms, or formulae. The explanation for these differences is probably to be found in the comparatively large number of subjects in our group and in the sharply restricted age range which has been studied previously only as part of younger or older groups.

PROCEDURE

The report is based on a cardiovascular survey of 2,600 school children in Pensacola, Florida, carried out as a joint study by the Florida State Board of Health and the U. S. Naval School of Aviation Medicine.[1] Seventy-six subjects were excluded from the analyses because of clinical or electrocardiographic evidence of actual or potential heart disease. Inasmuch as there were relatively few children younger than 12 or older than 17 (these subjects totaled 386 in number), they were also omitted. Thus, the analysis of the x-rays was confined to those of an adolescent group 12–17 years of age which included 2,138 subjects—1,072 boys and 1,066 girls. Approximately 50 per cent of these subjects had been born and raised in or near Pensacola; the rest had been born or had lived in various other parts of the United States or, in a few instances, in foreign countries.

Posteroanterior teleoroentgenograms of the chest were obtained at 6 foot tube-film distance using a portable 30 milliampere x-ray unit. The exposure varied from one-fourth to three-fourths second but was usually one-half second or less. The films were taken with the chest in the position of full inspiration. The following measurements and calculations were made:

(1) Transverse diameter of the heart (TD)—the sum of the maximum distances to the right and left cardiac borders from the midline.
(2) Long diameter of the heart—the distance from the cardiovascular junction on the right to the cardiac apex.
(3) Broad diameter of the heart—the greatest cardiac diameter drawn as an unbroken line perpendicular to the long diameter.
(4) Transverse diameter of the chest—the greatest internal diameter of the chest.
(5) Height of the heart—the vertical distance from the right end of the long diameter to the level of the apex of the left diaphragmatic leaf.
(6) Height of the chest—the highest point reached by the upper margin of the second left rib posteriorly to the level of the apex of the left diaphragmatic leaf.

* Part of a study at the U. S. Naval School of Aviation Medicine, Pensacola, Florida, conducted under the direction of Captain Ashton Graybiel, MC, USN, Director of Research. Opinions or conclusions contained in this report are those of the authors. They are not to be construed as necessarily reflecting the view or the endorsement of the Navy Department.

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TABLE I

Mean Height and Weight with Predicted Mean Weight for Each Age-Sex Group

Age	No. of cases	Mean height (inches)	Mean weight (pounds)	Predicted mean weight* (pounds)
		Boys		
12	102	59.7	92	91
13	153	62.5	105	105
14	142	64.9	118	118
15	215	67.6	132	132
16	244	68.6	139	140
17	216	69.8	148	148
		Girls		
12	131	60.4	94	97
13	149	62.5	106	108
14	161	63.3	109	114
15	186	64.2	115	119
16	212	64.4	118	121
17	227	64.3	117	123

* Baldwin and Wood.[3]

(7) The front area of the heart (FA) was read from the Ungerleider and Gubner nomogram[2] employing the long and broad diameters.

(8) The cardiothoracic ratio (C/T) was calculated by dividing TD by the transverse diameter of the chest.

Results

ANALYSES

The subjects were divided initially into groups by sex and then by age; this resulted in 12 age-sex groups, each composed of more than 100 subjects (Table I).

Height and Weight: The mean and standard deviations of the height and weight for each group were determined first. At age 12 the girls were slightly taller and heavier than the boys. By age 14, however, the boys were larger than the girls and with each succeeding year of age the difference became more pronounced The girls' height stabilized at age 15, and their weight at age 16. In order to see how closely the heights and weights of our subjects approximate those predicted for adolescents, we took the mean height for each age and sex and read

TABLE II

Means and Standard Deviations of C/T, TD, and FA

Age	Number	Cardiothoracic ratio		Transverse diameter in mm		Frontal area in cm^2	
		Mean	S.D.	Mean	S.D.	Mean	S.D.
				Boys			
12	102	0.4246	0.0294	106.14	9.39	96.35	13.56
13	153	0.4225	0.0336	110.17	10.25	105.86	15.28
14	142	0.4155	0.0313	113.33	10.21	111.10	14.85
15	215	0.4165	0.0390	116.81	12.68	119.25	16.50
16	244	0.4077	0.0392	116.05	11.36	119.88	15.77
17	216	0.4093	0.0393	118.95	12.36	123.20	16.59
				Girls			
12	131	0.4192	0.0288	102.29	9.75	91.65	11.23
13	149	0.4204	0.0339	105.02	11.04	98.70	13.11
14	161	0.4217	0.0299	105.56	9.87	103.05	14.18
15	186	0.4153	0.0337	105.09	10.12	101.89	12.61
16	212	0.4153	0.0348	106.33	11.55	102.43	14.42
17	227	0.4163	0.0350	105.78	10.15	102.56	13.98

the predicted weight from the table prepared by Baldwin and Wood.[3] Table I shows that in the case of the boys the weights were almost identical, but that the girls in our group were consistently a few pounds lighter than predicted.

Cardiothoracic Ratio (C/T): The mean cardiothoracic ratio was determined for each of the twelve age-sex groups (Table II). The mean plus or minus 2 standard deviations ranged from about 0.33 to 0.49 in both sexes. The means decreased very slightly (0.02) with increasing age in boys and showed no trend with age in girls. Boys and girls differed on the average by only 0.01 or 0.02 at each age. Only 12 (1 per cent) of the girls and 26 (2 per cent) of the boys had a C/T of 0.50 or greater.

Because the cardiothoracic ratio was only slightly affected by age or sex, the effects of body weight and height on C/T were studied in each age-sex group. Correlation coefficients for both height and weight with C/T were calculated, and it was evident that neither height nor weight was closely related to C/T, as the correlations ranged from −0.30 to +0.30. Thus, it appears that C/T is largely independent of age, sex, body height, or weight.

TABLE III

Per Cent of Subjects Whose Values for TD and for FA Deviated from Predicted*

	Total deviation more than 10 per cent (%)	Smaller than predicted (%)	Larger than predicted (%)
TD	25	22	3
FA	37	20	17
TD and FA	15	12	3
TD or FA	47	30	17

* TD predicted by Ungerleider and Clark.[4]
FA predicted by Ungerleider and Gubner.[2]

Transverse Diameter: Although many authors have devised prediction formulae for transverse diameter, we compared the cardiac measurements of our subjects first with those predicted by the widely accepted table of Ungerleider and Clark[4] whose subjects were 15 years of age and older. For each of our subjects a predicted TD was read from that table on the basis of the individual's height and weight. It was found that 22 per cent of our observed values were at least 10 per cent less than predicted and 3 per cent were at least 10 per cent greater than predicted, that is, above the upper limit of normal variation as delineated by those authors (Table III).

As an additional approach the predicted TD for each age-sex group was derived from the Ungerleider and Clark table by using the *mean* heights and weights for each of the twelve groups. Plotting age against per cent deviation of "observed" from "predicted" TD (Ungerleider) for each age-sex group yielded the curves shown in Figure 1. The mean TD

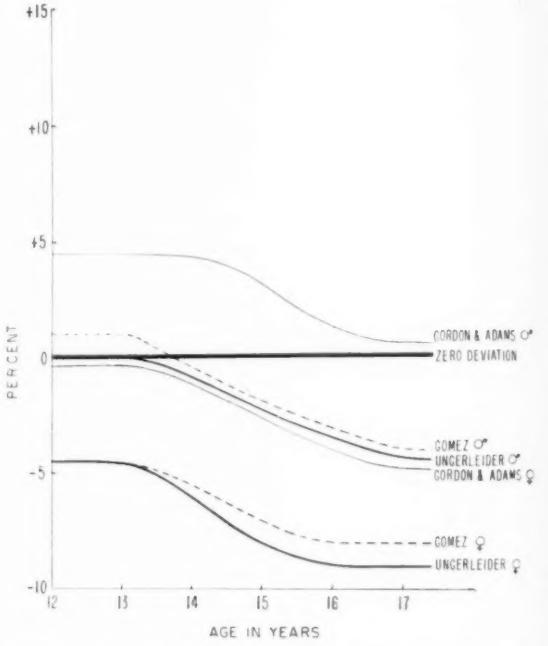

Fig. 1. Age vs. per cent deviation of observed from predicted TD.

of 12- and 13-year-old boys was predicted accurately by this formula. For 14- and 15-year-old boys it was progressively less accurate, and for 16- to 18-year-old boys the observed mean TD was about 5 per cent less than predicted. The curve for the girls was parallel to that for the boys, but the observed values varied with increasing age from 5 per cent less to 9 per cent less than predicted by this formula.

Gomez[5] modified the formula on which the Ungerleider and Clark prediction table for TD was based and recommended its use for children and adolescents. However, when the predicted TD for each of our 2,138 subjects was derived by the Gomez formula, it was found again that 3 per cent of these normal subjects had TD's more than 10 per cent greater than predicted and over 20 per cent of them had TD's more than 10 per cent smaller than predicted. Thus, it appeared that the Gomez formula offered no advantage over the Ungerleider and Clark table.

Plotting age against per cent deviation of observed from predicted TD (Gomez) for the 12 age-sex groups yielded curves almost identical in configuration and position to those obtained when the Ungerleider and Clark table was used (Fig. 1).

The formula of Gordon and Adams[6] for prediction of TD in children was studied also. Plotting age against per cent deviation of observed from predicted TD (Gordon and Adams) for our age-sex groups resulted in curves which deviated less than the curves derived by either of the two previous methods (Fig. 1); however, the configuration of the curves for both boys and girls was similar. The mean TD in older girls was 5 per cent larger than predicted while that in younger boys was 5 per cent smaller than predicted.

Frontal Area: One of the most widely accepted criteria for evalution of FA is the nomogram of Ungerleider and Gubner.[2] When this nomogram was used, 17 per cent of the *individual* subjects had a frontal area measurement more than 10 per cent greater than predicted while 20 per cent of them had values more than 10 per cent smaller than predicted (Table III). Plotting age against per cent deviation of observed from predicted *mean* FA (Ungerleider and Gubner) for each age-sex group resulted in the curves seen in Figure 2. The younger boys had FA's smaller by 5 per cent than predicted while the FA in the older boys was up to 2 per cent greater than should be expected by this method. The curve for the girls was not parallel to that for the boys. Although the FA's of the younger girls were predicted accurately by the nomogram, those of the older girls exceeded the predicted values by 4 per cent.

The formula derived by Hodges and his coworkers[7] for prediction of FA from the teleoroentgenogram in children was evaluated next. When applied to each of the age-sex groups, it consistently underpredicted the mean FA from 3 to 14 per cent (Fig. 2). Deviation from the

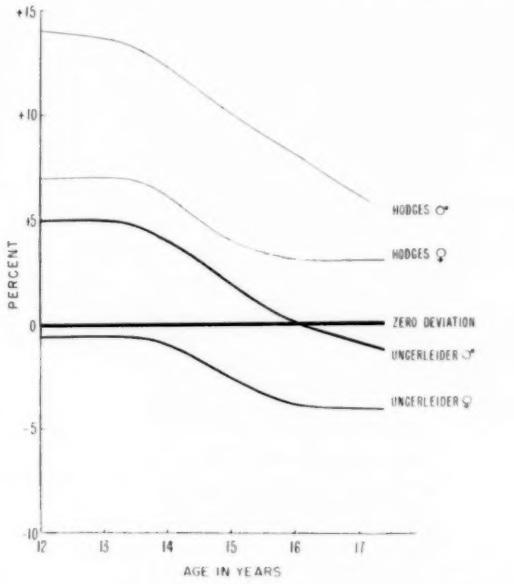

Fig. 2. Age vs. per cent deviation of observed from predicted FA.

predicted FA was greater in the younger subjects (7 per cent for girls and 14 per cent for boys) than it was in the older ones (3 per cent for girls and 5 per cent for boys).

Correlation of Various Factors with Cardiac Measurements: Since age and sex seemed to affect the preceding criteria, which were based on weight and height alone, it was decided to investigate the degree of correlation of various factors with cardiac measurements.

To determine the relationship between the mean cardiac measurements and age, an analysis of variance design was used. These analyses were done separately for the two sexes. The variations of mean TD and mean FA with age were significant at the 0.001 level of confidence in all cases except the TD of the girls; there the relationship was at the 0.05 level. Age is thus a variable which affects both TD and FA in boys, and FA in girls.

To determine the significance of the effects of sex on TD and FA, separate analyses of

TABLE IV

Product-Moment Correlations and Multiple Correlations (R) of Height and Weight with TD and FA

	Boys			Girls		
	Height	Weight	Height and weight (R)	Height	Weight	Height and weight (R)
TD	0.39	0.58	0.60	0.21	0.60	0.62
FA	0.62	0.68	0.69	0.41	0.57	0.58

variance were made for each age group as age already had been shown to be significant. At every age, differences between the sexes were statistically significant for both TD and FA.

Weight and height also proved to be related to TD and FA, as is seen by the correlation coefficients in Table IV. In general, weight was more closely related than height to both TD and FA. Furthermore, the correlations between weight and height were so high (0.60 to 0.80) that the addition of height to weight as a predictor resulted in a very small increment (i.e., the multiple R's were not much larger than the correlations between weight and TD or FA).

In view of these results, weight and height were used as covariants to adjust the differences found in the various age-sex groups and to determine whether these differences would "disappear" when weight and/or height were held constant. These analyses resulted in a reduction of the differences between the various groups, but there was still a significant variation. This led to the conclusion that sex and age must be used (at least in this age range) for accurate prediction of heart size.

Since, in the age-sex groups, height adds little to weight as a predictor of TD and FA, then the anthropometric index (W/H), used by Unger-

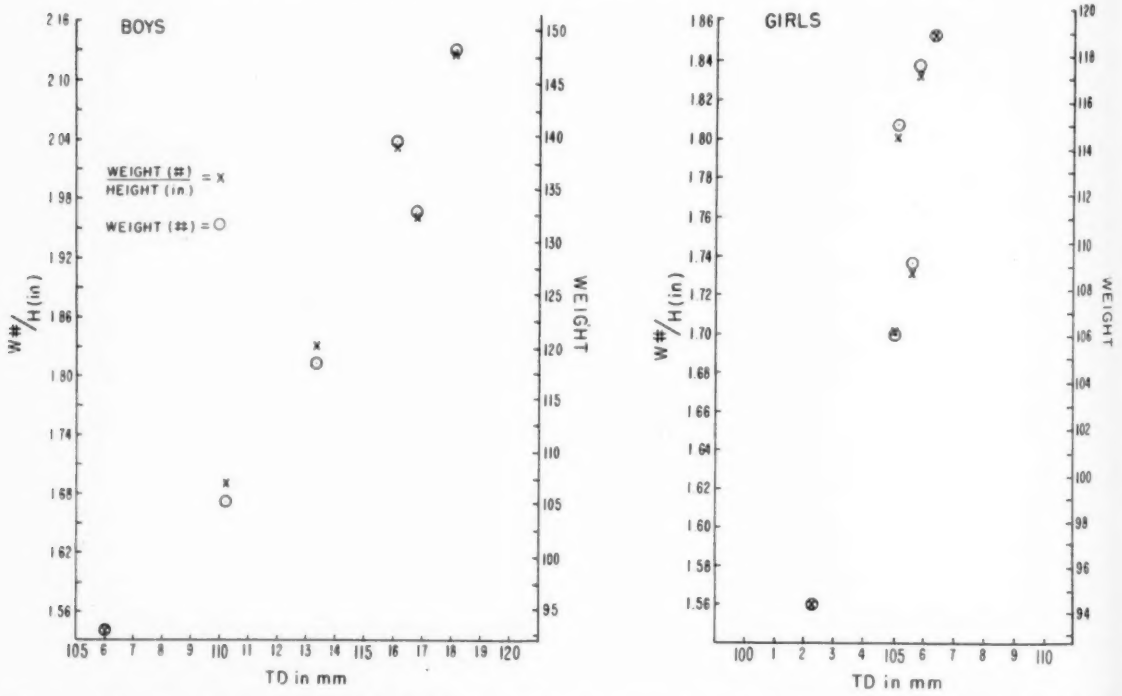

Fig. 3. Mean weight and mean weight/height for each age group plotted against TD. Note that the addition of height does not change the relationship.

leider in adults and by Gomez with children and adolescents, would appear to be of doubtful value once age and sex have been considered. As would therefore be expected, plotting the mean TD for each of the age-sex groups against the anthropometric index for each group resulted in the same curves as mean TD plotted against weight alone, as seen in Figure 3.

Correlations of cardiac height and of chest height with TD and FA were computed and found to be of low degree. No significant increase in the accuracy of prediction of cardiac size could be expected by addition of either of these factors to age, sex, and weight.

In the boys and the girls as groups, chest transverse diameter correlated better than, or as well as, body height with TD and FA. However, these correlations varied much more than did correlation of body height with these cardiac measurements. Since body height added so little to body weight in predicting the cardiac measurements, even less could be expected of chest transverse diameter in view of the wide variation in the correlations with the cardiac measurements.

Construction of the Tables

Separate prediction tables were prepared (see Table V) for each age-sex group inasmuch as the analyses described above had shown that there were differences between age groups and between sex groups even when the effects of weight and height differences were controlled. Weight alone was used as predictor because multiple correlation analyses had shown that height added very little to the multiple correlations. The upper and lower limits given (± 2 times the standard error of estimate) will include all but about 4.5 per cent of "normal" hearts, i.e., about 2.25 per cent will be found to exceed the upper limit and 2.25 per cent will be smaller than the lower limit. Full details of construction of the tables can be found in reference 8.

Use and Interpretation of the Tables

To obtain the predicted TD or FA for an individual in the age range 12 to 17, it is necessary to know only his age in years and weight in pounds. The appropriate table is then entered with the individual's weight, and the predicted value is read out from the center column. Transverse diameters are given in millimeters and frontal areas in square centimeters.

Of greater interest are the upper and lower limits given below the mean value. If an individual's heart is of normal size (for his age and weight), there is only a 2.25 per cent chance that it will exceed the upper limit given, and, similarly, there is only a 2.25 per cent chance that it will be below the lower limit. Hence, individuals whose heart measurements do fall outside these limits, especially the upper, are suspect, and the further out they are, the greater will be the likelihood of abnormality. At the same time, it is obvious that some abnormals may fall inside the normal range.

Extrapolations were made for weights above and below the usual range and should be regarded as somewhat less valid than those within the usual range.

Discussion

Although various authors have disputed the value of cardiac mensuration, we feel that it is a useful screening procedure for separating the probably normal from the probably enlarged and, therefore, abnormal heart. It is of greater importance in evaluating changes in cardiac status over a period of time as a permanent record can be kept. Fluoroscopy by a trained observer is a necessary adjunct to a complete cardiovascular examination, but because it depends on impressions rather than on measurements it loses some value in follow-up studies of the individual patient. Measurements of heart size can be made readily, not only with the 14 in. $\times$ 17 in. six-foot PA film of the chest but also with miniature films if the lead measuring device suggested by Ungerleider *et al.* be utilized.

It is appropriate here to include a brief discussion of the phase of respiration during which exposure of the x-ray should be made. It is generally conceded that the end of a normal inspiration, or "mid-inspiration," is the desired phase. Our experience with adolescents, however, led us to prefer exposure at the end of full inspiration because instructing the subject to stop breathing at any other time was time consuming and often impossible. Since exposure

TABLE V

TABLE FOR PREDICTING MEASUREMENTS OF HEART SILHOUETTE FOR VARIOUS AGES AND WEIGHTS OF ADOLESCENT BOYS BASED ON SAMPLE OF 1072 BOYS

BOYS

Transverse Diameter in Millimeters — Mean, Lower & Upper Limits of Normal							Frontal Area in Square Centimeters — Mean, Lower & Upper Limits of Normal					
AGE (in years)						WEIGHT IN POUNDS	AGE (in years)					
12	13	14	15	16	17		12	13	14	15	16	17
80-116	79-115					60	56-112	59-115				
81-117	80-116	79-115	77-113			65	58-114	61-117	63-119	64-120		
83-119	82-118	80-116	78-114	76-112	74-110	70	60-116	63-119	65-121	66-122	66-122	66-122
84-120	83-119	82-118	80-116	78-114	75-111	75	62-118	65-121	67-123	68-124	68-124	68-124
85-121	85-121	83-119	81-117	79-115	77-113	80	64-120	67-123	69-125	70-126	70-126	70-126
87-123	86-122	85-121	83-119	81-117	79-115	85	66-122	69-125	71-127	72-128	72-128	72-128
88-124	87-123	86-122	85-121	83-119	81-117	90	68-124	71-127	73-129	73-129	74-130	74-130
89-125	89-125	88-124	86-122	84-120	82-118	95	70-126	73-129	74-130	75-131	76-132	76-132
91-127	90-126	89-125	88-124	86-122	84-120	100	72-128	75-131	76-132	77-133	78-134	78-134
92-128	92-128	91-127	89-125	88-124	86-122	105	74-130	77-133	78-134	79-135	80-136	81-137
94-130	93-129	92-128	91-127	89-125	88-124	110	76-132	79-135	80-136	81-137	81-137	82-138
95-131	95-131	94-130	93-129	91-127	89-125	115	78-134	81-137	82-138	83-139	83-139	84-140
96-132	96-132	95-131	94-130	93-129	91-127	120	80-136	83-139	84-140	85-141	85-141	86-142
98-134	98-134	97-133	96-132	94-130	93-129	125	82-138	84-140	86-142	87-143	87-143	88-144
99-135	99-135	98-134	97-133	96-132	94-130	130	84-140	86-142	88-144	89-145	89-145	90-146
100-136	100-136	100-136	99-135	98-134	96-132	135	86-142	88-144	90-146	91-147	91-147	92-148
102-138	102-138	101-137	101-137	99-135	98-134	140	88-144	90-146	92-148	93-149	93-149	94-150
103-139	103-139	103-139	102-138	101-137	100-136	145	90-146	92-148	94-150	95-151	95-151	96-152
104-140	105-141	104-140	104-140	103-139	101-137	150	92-148	94-150	96-152	97-153	97-153	98-154
106-142	106-142	106-142	105-141	104-140	103-139	155	94-150	96-152	98-154	99-155	99-155	99-155
107-143	108-144	107-143	107-143	106-142	105-141	160	96-152	98-154	100-156	101-157	101-157	101-157
109-145	109-145	109-145	109-145	108-144	107-143	165	98-154	100-156	102-158	103-159	103-159	103-159
110-146	111-147	111-147	110-146	109-145	108-144	170	100-156	102-158	104-160	105-161	105-161	105-161
	112-148	112-148	112-148	111-147	110-146	175		104-160	106-162	107-163	107-163	107-163
	113-149	114-150	113-149	113-149	112-148	180		106-162	108-164	109-165	109-165	109-165
	115-151	115-151	115-151	114-150	114-150	185		108-164	110-166	111-167	111-167	111-167
		117-153	117-153	116-152	115-151	190			112-168	113-169	113-169	113-169
		118-154	118-154	118-154	117-153	195			114-170	115-171	115-171	115-171
		120-156	120-156	119-155	119-155	200			116-172	117-173	117-173	117-173
			121-157	121-157	121-157	205				119-175	119-175	119-175
			123-159	123-159	122-158	210				121-177	121-177	121-177
				124-160	124-160	215					123-179	123-179
				126-162	126-162	220					125-181	125-181
					128-164	225						127-183

at the end of full inspiration is the usual technic in taking routine chest films, our table can thus be used to interpret heart size on the standard six-foot PA film of the chest. (It is probable that Ungerleider's table is used most often on x-rays taken at full inspiration.) Before adopting this technic we explored the possible errors it might introduce. It would seem that the TD might be decreased with deeper inspiration and that the FA might be increased, since more of the lower border of the heart might be visible with lowered diaphragms. In actual practice the effect was negligible. When our values for TD and FA were compared with those

TABLE V *Continued*

TABLE FOR PREDICTING MEASUREMENTS OF HEART SILHOUETTE FOR VARIOUS AGES AND WEIGHTS OF ADOLESCENT GIRLS BASED ON SAMPLE OF 1066 GIRLS

GIRLS

Transverse Diameter in Millimeters — Mean; Lower & Upper Limits of Normal							Frontal Area in Square Centimeters — Mean; Lower & Upper Limits of Normal					
AGE (in years)						WEIGHT IN POUNDS	AGE (in years)					
12	13	14	15	16	17		12	13	14	15	16	17
90 (74-106)	90 (74-106)					60	71 (56-100)	71 (59-103)				
87 (76-108)	87 (76-108)	88 (73-105)	88 (73-105)			65	80 (58-102)	82 (61-105)	83 (63-107)	82 (61-105)		
84 (78-110)	84 (78-110)	84 (75-107)	89 (74-106)	88 (73-105)	88 (73-105)	70	84 (60-104)	84 (63-107)	85 (65-109)	84 (63-107)	84 (62-106)	84 (62-106)
85 (79-111)	85 (79-111)	87 (77-109)	85 (75-107)	85 (75-107)	85 (75-107)	75	87 (62-106)	87 (65-109)	88 (67-111)	87 (65-109)	86 (64-108)	86 (65-108)
87 (81-113)	87 (81-113)	85 (79-111)	87 (77-109)	87 (76-108)	87 (76-108)	80	86 (64-108)	88 (67-111)	90 (68-112)	88 (67-111)	88 (66-110)	88 (66-110)
89 (83-115)	89 (83-115)	86 (80-112)	85 (79-111)	84 (78-110)	84 (78-110)	85	88 (66-110)	91 (69-113)	93 (70-114)	91 (69-113)	90 (68-112)	90 (68-112)
91 (85-117)	91 (85-117)	88 (82-114)	89 (81-113)	86 (80-112)	86 (80-112)	90	90 (68-112)	93 (71-115)	94 (72-116)	93 (71-115)	92 (70-114)	92 (70-114)
93 (86-118)	93 (86-118)	90 (84-116)	88 (82-114)	88 (82-114)	88 (82-114)	95	92 (70-114)	95 (73-117)	96 (74-118)	94 (72-116)	94 (72-116)	94 (72-116)
94 (88-120)	94 (88-120)	92 (86-118)	90 (84-116)	89 (83-115)	89 (83-115)	100	94 (72-116)	97 (75-119)	98 (76-120)	97 (75-119)	96 (74-118)	96 (74-118)
96 (90-122)	96 (90-122)	93 (87-119)	92 (86-118)	91 (85-117)	91 (85-117)	105	96 (74-118)	99 (77-121)	100 (78-122)	98 (76-120)	98 (76-120)	98 (76-120)
98 (92-124)	98 (92-124)	95 (89-121)	94 (88-120)	93 (87-119)	93 (87-119)	110	97 (75-119)	101 (79-123)	102 (80-124)	100 (78-122)	100 (78-122)	99 (77-121)
99 (93-125)	99 (93-125)	97 (91-123)	95 (89-121)	94 (88-120)	94 (88-120)	115	99 (77-121)	103 (81-125)	104 (82-126)	102 (80-124)	101 (79-123)	101 (79-123)
101 (95-127)	101 (95-127)	99 (93-125)	97 (91-123)	96 (90-122)	96 (90-122)	120	101 (79-123)	105 (83-127)	106 (84-128)	104 (82-126)	103 (81-125)	103 (81-125)
103 (97-129)	103 (97-129)	100 (94-126)	99 (93-125)	98 (92-124)	98 (92-124)	125	103 (81-125)	107 (85-129)	108 (86-130)	106 (84-128)	105 (83-127)	105 (83-127)
104 (98-130)	104 (98-130)	102 (96-128)	101 (95-127)	100 (94-126)	100 (94-126)	130	105 (83-127)	109 (87-131)	110 (88-132)	108 (86-130)	107 (85-129)	107 (85-129)
106 (100-132)	106 (100-132)	104 (98-130)	102 (96-128)	102 (96-128)	101 (95-127)	135	107 (85-129)	111 (89-133)	112 (90-134)	110 (88-132)	109 (87-131)	109 (87-131)
108 (102-134)	108 (102-134)	106 (100-132)	104 (98-130)	103 (97-129)	103 (97-129)	140	109 (87-131)	113 (91-135)	114 (92-136)	112 (90-134)	111 (89-133)	111 (89-133)
110 (104-136)	110 (104-136)	107 (101-133)	106 (100-132)	105 (99-131)	105 (99-131)	145	111 (89-133)	115 (93-137)	116 (94-138)	114 (92-136)	113 (91-135)	113 (91-135)
111 (105-137)	112 (106-138)	109 (103-135)	108 (102-134)	108 (102-134)	107 (101-133)	150	113 (91-135)	117 (95-139)	118 (96-140)	116 (94-138)	115 (93-137)	115 (93-137)
	113 (107-139)	111 (105-137)	109 (103-135)	108 (102-134)	108 (102-134)	155		118 (96-140)	120 (98-142)	118 (96-140)	117 (95-139)	117 (95-139)
	115 (109-141)	113 (107-139)	111 (105-137)	110 (104-136)	110 (104-136)	160		120 (98-142)	122 (100-144)	120 (98-142)	119 (97-141)	119 (97-141)
		114 (108-140)	113 (107-139)	112 (106-138)	112 (106-138)	165			124 (102-146)	122 (100-144)	121 (99-143)	121 (99-143)
			115 (109-141)	114 (108-140)	114 (108-140)	170				124 (102-146)	123 (101-145)	123 (101-145)
				115 (109-141)	115 (109-141)	175					125 (103-147)	125 (103-147)
					117 (111-143)	180						127 (105-149)

Directions for use: Find the nearest weight in the center column and read across to value under proper age to obtain the predicted Transverse Diameter, or the Frontal Area. Only 4.5 per cent of normals will have values larger or smaller than the limits shown in Roman type (±2 standard error of estimate).

predicted by the criteria of various authors who used mid-inspiration for exposure, no statistically significant trend could be found to indicate that we had introduced an error.

The question of which measurement is "best," TD, FA, or C/T, arises often. We believe that the TD is superior to the other two for the following reasons: (1) The TD is ascertained quickly by one application of the ruler; (2) the interpretation of the figure is not time

consuming if the height and weight of the subject are available for use in a table such as that published by Ungerleider for adults, or if the age, sex, and weight are available for use in the tables presented in this paper for adolescents. The FA, in contrast, is inherently more variable and also requires two measurements which in most cases are not sharply defined but depend largely on intuition. The figures obtained may be substituted in a formula or may be used in a nomogram to obtain the actual FA and its deviation from the predicted normal for a person of the same height and weight. We believe that the method is too cumbersome for routine use and that it does not add sufficient accuracy to cardiac mensuration to warrant its use in place of the TD.

For the cardiologist or radiologist a table of normal values is greatly to be preferred over a formula; in our experience the use of a formula is so time consuming that it is not practical for clinical use. The cardiothoracic ratio has several advantages: ease of measurement, knowledge of the subject's height and weight is not required, and the avoidance of tables or nomograms. However, it is a crude measure which fails to detect slight cardiac enlargement and is unnecessary for identification of grossly enlarged hearts; therefore, it is of slight value to the clinician.

Summary

Measurements of heart size were made from the teleoroentgenograms of 2,138 healthy school children 12 through 17 years of age. There were 1,072 boys and 1,066 girls studied, none of whom had clinical or electrocardiographic evidence of heart disease.

Extensive statistical studies were carried out with the following results: (a) Age, sex, and body weight were the most important variables in determining heart size in these adolescents; (b) body height and certain chest measurements did not correlate very highly with heart size; (c) transverse diameter of the heart was less variable and therefore in some ways a more preferable measurement than either frontal area or cardiothoracic ratio; (d) none of the presently available tables, formulas, or nomograms for predicting TD or FA is adequate for adolescents because none of them uses age or sex as variables.

Prediction tables for transverse diameter and frontal area of the heart in adolescents have been prepared using age, sex, and weight as the variables. Use of these variables should result in better predictions than those obtained by other presently available methods.

Acknowledgments

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The Riddle of the Labile T Wave*

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With the technical assistance of Janet C. Lloyd

THE CLASSIC "juvenile pattern" and its latent variant elicited by brief hyperventilation may well be the key to the understanding of the labile T wave. The reproducibility of this pattern lends itself to a variety of experimental approaches.[1–3]

It is the purpose of this paper to present a number of "latent juvenile patterns" observed during the past 12-month period which demonstrate striking similarity. The magnitude of the T wave changes is the basis for our selection of these patients. Also documented is the role of emotional stress producing marked T wave changes.

MATERIAL AND METHODS

The 12 negro patients included in the present report were seen at the VA Hospital, Madison, Wisconsin, between June 1956 and July 1957. All were hospitalized for treatment of pulmonary tuberculosis and to date, all but two have been discharged with inactive disease. There was an age range from 25 to 39 years. All patients were subjected to hyperventilation in a recumbent position for a 10 to 15 second period during the recording of each precordial unipolar lead. Only frank T wave inversions of 2 mm or more during this period are included in the reproductions. Hyperventilation repeated at various intervals during the hospital stay of the patients consistently reproduced the T wave changes. Numerous follow-up electrocardiograms and various drug studies were completed on individual patients; they are not included in the present study.

RESULTS

The effect of hyperventilation in the evolution of latent T wave changes is shown in Figures 1, 2 and 3. The relative uniformity of the T wave inversion pattern in the mid and left precordial leads is apparent. The point of T wave inversion occurs at the junction of the terminally notched T wave and succeeding U wave. In general, short QT intervals were observed with long diastolic filling periods (T-P interval). There was no appreciable shift of the RST segment except in a single instance (lead V_3 of patient H. B., age 39), where the RST segment was depressed.

The effect of an apparent "alarm reaction" is shown in Figure 4. The patient was a young negro male who was extremely fearful of "needles." The anticipation response of marked T wave inversion occurred when the skin was merely rubbed with alcohol. The ameliorating effect of reassurance on the T wave change is apparent.

DISCUSSION

One can only speculate on the ultimate role of emotional tension and hyperventilation, either induced or involuntary, on the extremely labile T wave of the adult electrocardiogram. In previous studies[1,2] it was shown that the hyperventilation effect was consistently abolished during vagal blockade and by the oral ingestion of potassium salts. In addition, this phenomenon appeared to operate independently of changes in gaseous content of the inspired air, i.e., respiratory alkalosis.[3]

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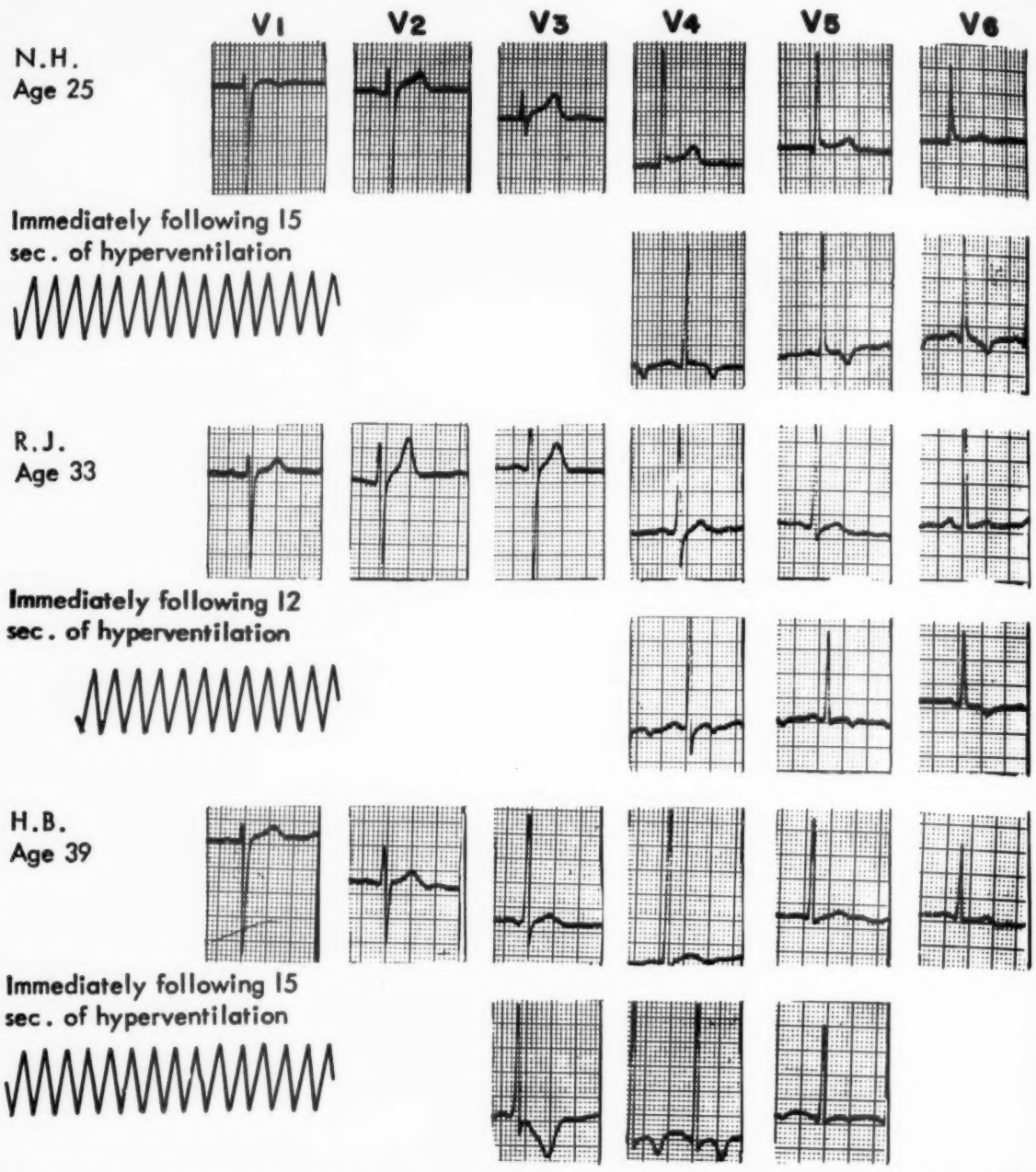

Fig. 1. T wave inversion following brief hyperventilation is clearly shown over the left ventricular leads. Lead V_3 showed slight RST segment depression following brief hyperventilation in patient H. B.

At present the mechanism for these marked T wave changes is lacking. The hyperventilation effect may perhaps be explained as a vagal reflex similar to the Hering-Breuer reflex, induced by the mechanical act of deep breathing. We have recently observed several patients with extremely active hyperventilation reflexes in whom a single maximum deep inspiration and expiration resulted in profound T wave inversion (Fig. 5). It has been suggested that the T wave changes are merely due to shift in cardiac position induced by respiration. This point of view does not appear to be tenable since additional exploratory leads in a vertical direction yield similar T wave inversion patterns. Simonson[4] has compiled data on T wave inversion fol-

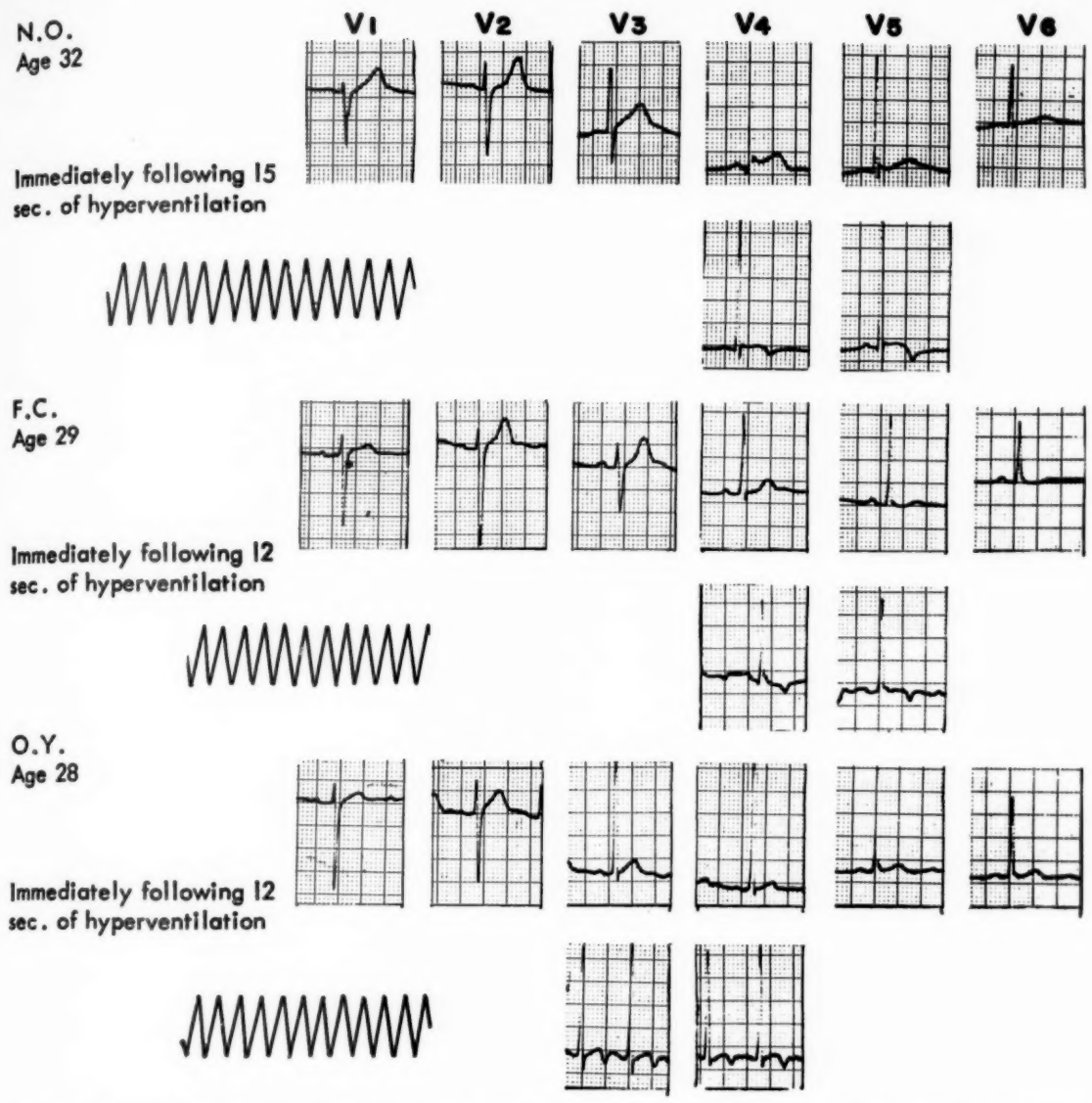

Fig. 2. Marked T wave inversion simulating organic change is seen to occur over the left ventricular leads following brief hyperventilation.

lowing deep breathing by means of vector analysis. His findings indicate that the reversal in T wave polarity operates independently of positional changes and, in addition, the presence of a direct vagal effect was questioned. Grant[5] has noted the presence of isolated areas of precordial T wave negativity in apparently normal young adults. Local electrical forces generated by the impact of the contracting heart against the anterior chest wall was suggested as a mechanism.

Thus, it appears that a more direct "cellular approach" to the observed electrocardiographic changes will be necessary to clarify the mysteries of the "juvenile pattern." Perhaps study of the coronary sinus blood for metabolic changes before, during and after brief hyperventilation might prove fruitful.

Regardless of the mechanism, the clinician's attention should remain focused on both overt and latent expressions of the "juvenile pattern" to avoid unnecessary implication of serious

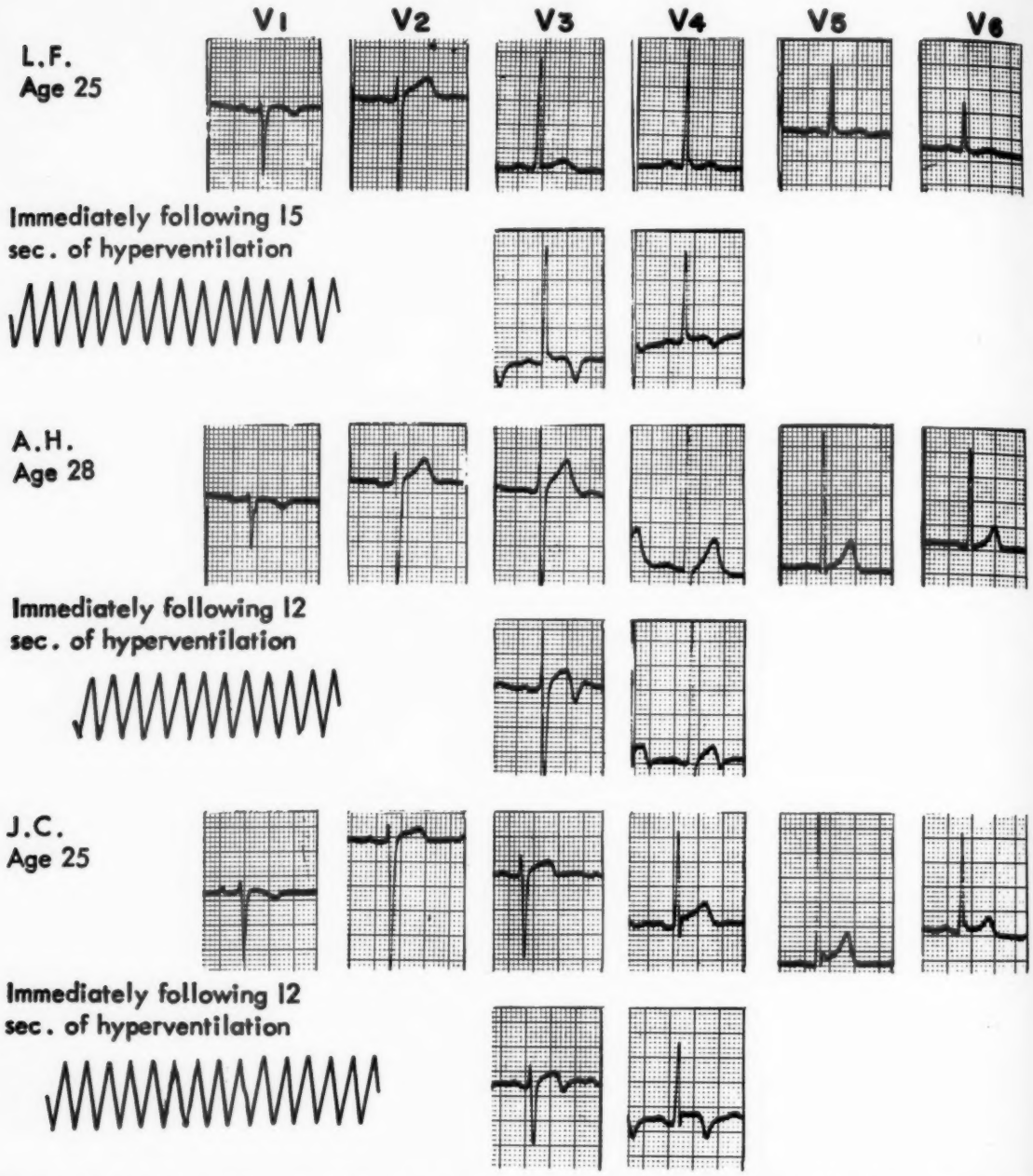

Fig. 3. Marked T wave changes are shown in the mid and left precordial leads following brief hyperventilation.

organic heart disease. Conversely, the pendulum must not be permitted to swing so far that all minor or fluctuating T wave changes are considered "functional."

In general, the "juvenile pattern" is normalized by reassurance, sedation or vagal blockade and is exaggerated by brief hyperventilation. The pattern is reproducible.

Summary

(1) Additional examples of classic latent juvenile patterns are presented showing the characteristic T wave inversion which on occasion may be extreme.

(2) In general, there is evidence of a short QT interval and relatively prolonged T-P segment.

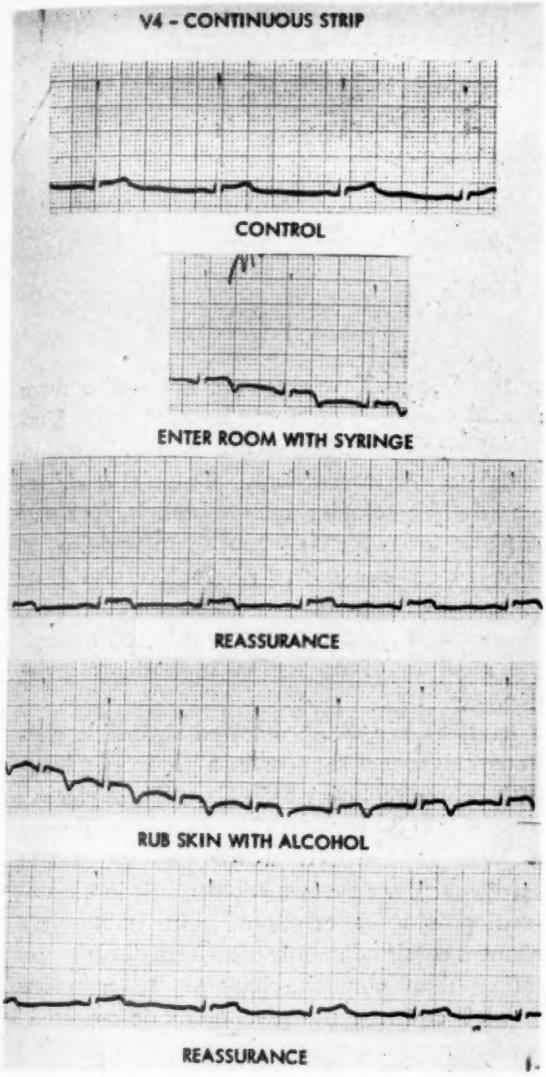

Fig. 4. The reproduction of marked T wave changes following an apparent "alarm reaction" is seen. Hyperventilation produced similar T wave changes on numerous instances in follow-up studies.

(3) The T wave inversion may be present in either the mid or left precordial leads, is reproducible by means of brief hyperventilation, and simulates severe organic myocardial disease.

(4) It is hoped that by continued focus upon this challenging aspect of clinical electrocardiography, additional effort will be made to clarify the mechanism of this phenomenon.

Acknowledgments

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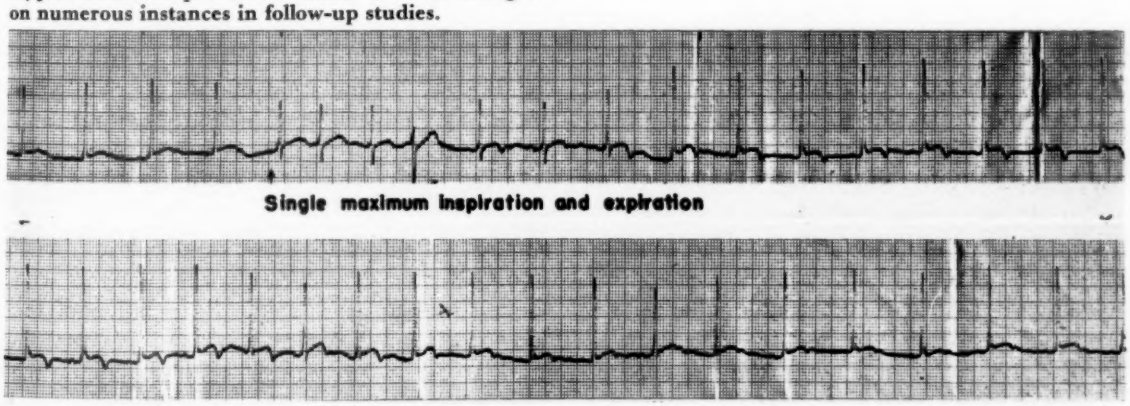

Fig. 5. The effect of a single maximum inspiration and expiration is shown on a continuous strip of lead V_4. Following maximum T wave inversion there is a gradual return to a diphasic T wave.

The Effect of the Psyche upon the Electrocardiogram

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EVER SINCE the first electrocardiogram was recorded in 1887 our knowledge of the extracardiac influences which could produce an abnormal record has been greatly expanded. At first the abnormal electrocardiogram was considered a *sine qua non* of organic heart disease. More recently leading investigators have repeatedly shown that not only could the electrocardiogram be normal in the presence of organic heart disease, but could also be abnormal in the absence of heart disease. In 1946 Sensenbach[1] listed 56 separate extracardiac entities associated with electrocardiographic abnormalities. Altered or abnormal emotional states were included.

A review of the medical literature by Blom[2] reveals an extensive bibliography corroborating the evidence that altered emotional states could influence the contour and rhythm of the electrocardiogram. Perhaps the earliest report was by Hyde and Scalapino[3] who in 1918 recorded varying amplitudes of the R wave in lead II in an individual subjected to different types of music. Other articles[4,5] have appeared with electrocardiograms taken in individuals having no evidence of organic heart disease before and after surgery. Many of these patients showed abnormal electrocardiograms before surgery with complete reversion to normal after surgery. The abnormalities were not only in varying voltage of the QRS complex, but in heart rate and in the ST-T complex. It was felt that fear of the forthcoming operation was the contributing cause of these alterations. Loftus and his co-workers[6] reported comparable changes in psychiatric patients subjected to extreme emotional disturbances and noted the presence of anxiety in these cases. At times the changes in the Q and T waves were not unlike those seen in transitory coronary insufficiency. Similar changes have been recorded in patients subjected to startle reactions. Graybiel *et al.*[7] reported one case of left bundle branch block that persisted for two days when a gun was fired at close range unexpectedly. It has also been known that changes in electrocardiographic contour and rhythm could be effected through the medium of suggestion in patients under hypnosis.

In 1946 Wendkos[8] reported reversible electrocardiographic changes in a group of soldiers with neurocirculatory asthenia. These changes were primarily contour changes of the T wave in leads II and III. Katz[9] also stated that cardiovascular neuroses could result in electrocardiographic aberrations, but that these changes consisted mainly of rhythm disturbances rather than contour changes. In a review article[10] covering the psychosomatic aspects of cardiac arrhythmias published in 1947 he cited experimental evidence showing the effects of the hypothalamus and cortex on the cardioregulatory centers of the brain. For example, faradic stimulation of the cortex adjacent to the precentral sulcus evoked marked alterations in heart rate. Stimulation of the anterior hypothalamus produced slowing of the heart rate and prolongation of the P-R interval. A possible clinical counterpart of these observed experimental changes is the report by Dry[11] who described prolonged P-R intervals, prolongation of the QRS and even S-A block in patients with neurocirculatory asthenia. Stimulation of the posterior hypothalamus produced tachycardia and frequent premature systoles. It is the general consensus that the common neural path-

ways to the heart are the vagus and accelerator nerves to the heart from the higher autonomic centers in the brain.

Psychic influence upon the function of the heart and secondarily on the electrocardiogram may also be mediated through alteration in the endocrine system. Emotional states may produce changes in body chemistry which may in turn affect the electrocardiogram. Production of alkalosis in normal young adults by hyperventilation has resulted in low voltage of T waves and depression of the ST segments in the limb leads. Hypoglycemia due to overactivity of the pancreas or insulin overdosage is attended by increased heart rate and electrocardiographic changes suggestive of coronary insufficiency. Cases of spontaneous hypoglycemia have been reported with associated ST segment and T wave changes. These changes reverted to normal upon correction of the hypoglycemic state. Bellet *et al.*[12] showed marked changes in the electrocardiogram of 38 out of 59 patients who underwent insulin shock therapy. All 59 patients had pre-treatment electrocardiograms which were within normal limits.

Adrenalin released during sudden and excessive emotional excitation directly affects cardiac function. Electrocardiographic effects are noted mainly in the acceleration of the cardiac rate, production of premature systoles and in T wave changes. Hartwell *et al.*,[13] studying the effects of various autonomic drugs on four normal subjects, concluded that adrenergic compounds lowered T waves while cholinergic compounds had the opposite effect. Wendkos and Logue[8] tended to support this hypothesis in cases of neurocirculatory asthenia by demonstrating the absence of these T wave changes after administration of ergotamine tartrate or atropine sulfate. In addition they were able to abolish the orthostatic T wave abnormalities seen in electrocardiograms taken in the upright position by injection of ergotamine. Female sex hormones also seem to have an indirect effect on the electrocardiogram. Scherf[14] observed electrocardiographic changes in menopausal women with subsequent reversal of these changes upon administration of follicular hormones. As stated by Katz:[10] "It would thus appear from the evidence presented that cardiac arrhythmias (and changes in contour) can result from imbalance either of the autonomic

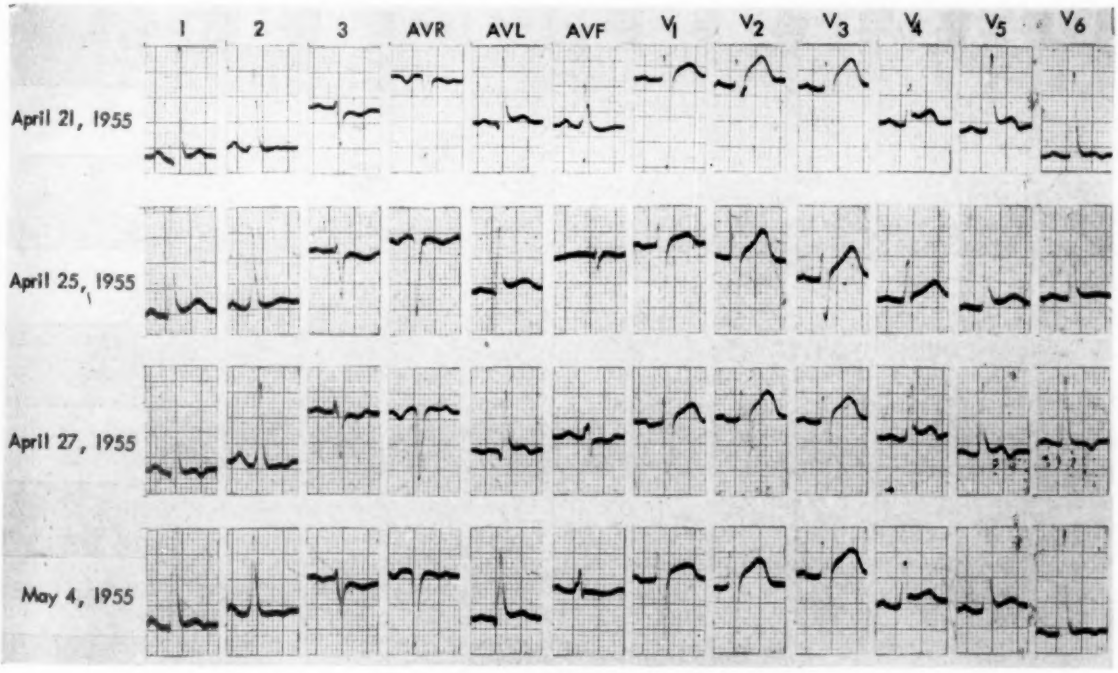

Fig. 1. Electrocardiograms of case 1.

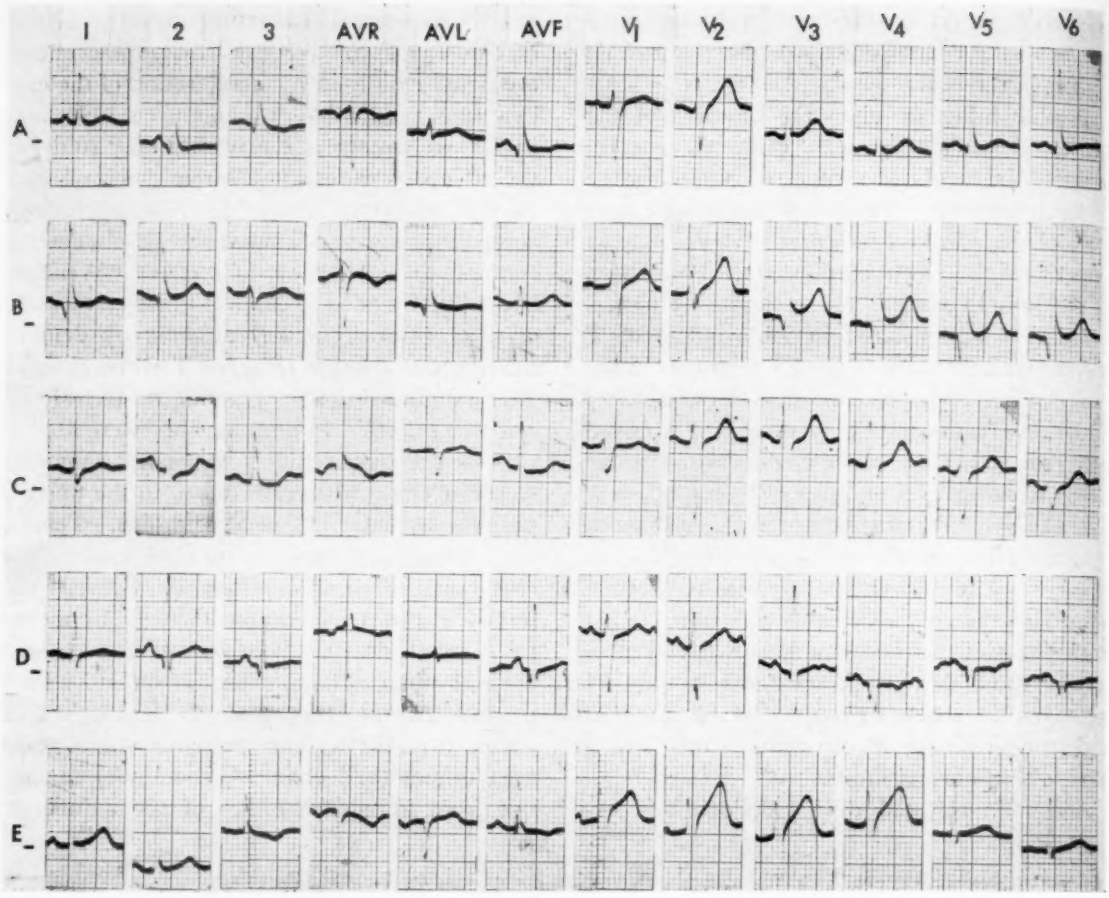

Fig. 2A. Electrocardiograms of case 2. (B) case 3. (C) case 4. (D) case 5. (E) case 6.

nervous system or from imbalance of the endocrine system and that these two systems are inter-related in rather complex ways."

Further proof has been offered that abnormal emotional states may be attended by abnormal electrocardiograms in the absence of organic heart disease. In 1947, Heyer *et al.*[15] compared the electrocardiograms of 200 physically normal, psychotic patients with a control group of 200 entirely normal patients. In routine preshock electrocardiograms 21.5 per cent of the psychotic patients showed abnormalities as compared to 6 per cent of the control group. These abnormalities consisted of T wave changes, prolongation of the P-R interval and more rarely, prolongation of the QRS complex. Changes were also reported in cases of manic depressive psychosis and in the catatonic and hebephrenic types of schizophrenia where no heart disease could be demonstrated clinically.

Case Histories

In the course of reading electrocardiograms at a local hospital numerous instances of abnormal records were noted in psychotic patients prior to shock therapy. Perhaps the most interesting set of tracings were those recorded in the first case.

Case 1. (Fig. 1). J. V., a 22-year-old WW II veteran of Spanish descent, was admitted to the local Veterans Administration Hospital for psychiatric therapy because of manic depressive psychosis. On April 21, 1955 a routine electrocardiogram showed changes indicative of pericarditis. The changes, most evident in the leads over the left precordium, showed ST elevation in V_4 and V_5 with inverted T waves in V_5 and V_6. In addition, the R/T ratio was definitely abnormal in leads I and

II. Shock therapy was delayed while the patient underwent a complete medical examination. No symptoms or signs could be elicited indicative of cardiovascular involvement nor was any history obtained of past illness which could have served as a predisposing cause of cardiac disease. All laboratory tests were normal.

A repeat electrocardiogram four days later (April 25, 1955) showed marked changes toward normal. The only abnormality noted was the flattening of the T wave in V_6. Of note was the change in the electrical axis of the heart from an intermediate position to a horizontal position (see aVF). Two days later (April 27, 1955) the patient showed marked psychotic tendencies. A repeat electrocardiogram again showed marked abnormalities suggestive of an acute diffuse pericarditis. Once again, physical examination revealed no evidence of cardiovascular involvement. In the last tracing taken one week later (May 4, 1955), the pericarditis pattern was still evident, but not as remarkable as in the previous record. It was finally decided that the patient did not have organic heart disease and that there was no cardiac contraindication to shock therapy. No adverse physical effects were noted after shock treatment. The patient was discharged shortly thereafter and unfortunately a post-shock electrocardiogram was not obtained.

Case 2. (Fig. 2A). S. B., a 42-year-old WW II veteran with schizophrenia and no organic heart disease. This electrocardiogram was considered abnormal because of flattening of T in lead II with an abnormal R/T ratio, diphasic T in aVF and flattening of T in V_6.

Case 3. (Fig. 2B). C. J. K., a 34-year-old WW II veteran with schizophrenia and no organic heart disease. This electrocardiogram shows nonspecific abnormalities as manifested in T inversion in aVL and the deep Q waves in V_4, V_5 and V_6.

Case 4. (Fig. 2C). D. D., a 26-year-old WW II veteran with manic-depressive psychoses and no organic heart disease. The electrocardiogram showed ST depression in II, III and aVF.

Case 5. (Fig. 2D). R. E. G., a 28-year-old WW II veteran with paranoia. No evidence of organic heart disease. The abnormalities of the T wave are evident in V_5–V_6. A repeat electrocardiogram subsequent to shock therapy was within normal limits.

Case 6. (Fig. 2E). R. H., a 34-year-old Negro WW II veteran with schizophrenia but no organic heart disease. The electrocardiographic abnormality was the slight ST depression and T wave inversion in III and aVF. Without knowledge of the patient's condition, the electrocardiographer interpreted the tracing as showing left heart strain in a vertically placed heart.

Conclusion

The practical implications that can be drawn from these observations are obvious. An unequivocal diagnosis of organic heart disease should not be made on the basis of electrocardiographic abnormalities alone. In this way one form of iatrogenic heart disease can be avoided. The electrocardiogram, when properly utilized and evaluated, can serve as a valuable laboratory aid; when interpreted in total ignorance of the patient's clinical condition, it can serve only as a source of confusion and diagnostic indecision. Winton and Wallace[16] stated: "Based upon the objective consideration of the electrocardiogram alone without proper clinical evaluation of the patient's cardiovascular status, a diagnosis of heart disease could easily have been made."

However, all ST-T changes in electrocardiograms of psychotic individuals should not be minimized for an occasional case of asymptomatic coronary sclerosis with associated myocardial damage may be missed.

As Magendantz and Shortsleeve[17] write: "It is not suggested that all slight RS-T and T changes be cast off lightly, but rather that the interpreter be cautious in his conclusions. We recommend in all such cases that the electrocardiogram be repeated after reassurance and 15 minutes of rest." In a greater percentage of cases, this procedure will result in complete reversibility of ST-T abnormalities with return of the electrocardiogram to normal.

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Experimental Studies

Cardiac Drug Responses and Potassium Shifts

Studies on the Interrelated Effects of Drugs on Coronary Flow, Heart Action and Cardiac Potassium Movement (Section II)*

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II. OBSERVATIONS ON THE EFFECTS OF CARDIAC DEPRESSANTS ON CORONARY FLOW, HEART ACTION AND ASSOCIATED POTASSIUM MOVEMENT IN THE HEART

It appeared from the previous experiments that loss of potassium from the heart might be an important factor in the production of the stimulated heart activity induced by the various cardiac stimulants. It was therefore of interest to investigate similarly a number of cardiac depressant drugs, and in this connection some observations on the effects of injections of acetylcholine and nitroglycerin are presented.

Acetylcholine: Figure 10 shows effects of an injection (AC) of 100 μg of acetylcholine, as observed in a typical experiment.

Under these conditions (upper kymograph record) there was a slight initial decrease followed by a sustained increase in coronary inflow; the heart contractions were promptly arrested with occasional beats as shown on the tracing, but relatively normal contractions were soon restored. During the initial inhibition there was a definite "net gain" of potassium by the heart (middle graph), which declined progressively. The concomitant electrograms (lower records) taken at A to H, demonstrate the well known initial pacemaker slowing of the heart with temporary ventricular asystole, followed by varying degrees of A-V block (B, C, and D). Whereupon, prompt restoration to a normal pattern followed (E to H). Similar results were obtained in six experiments.

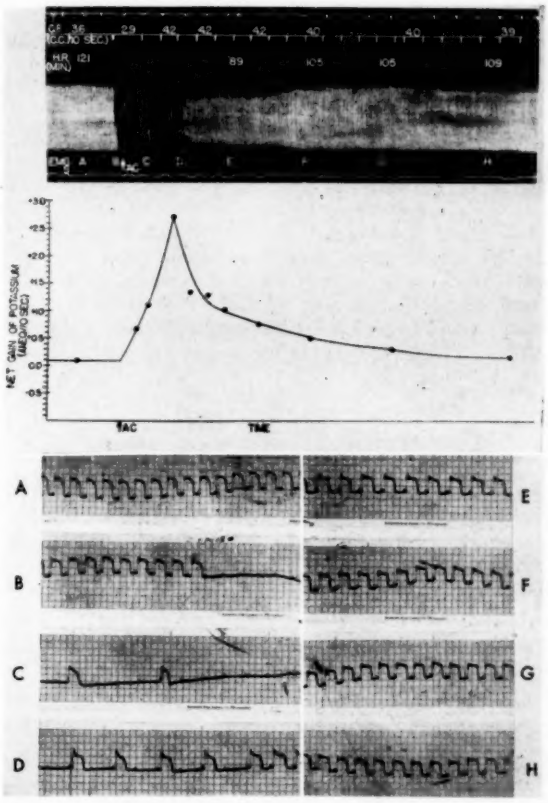

Fig. 10. Isolated rabbit heart perfused with normal Locke's solution. Upper Record: At arrow, AC, 100 μg of acetylcholine injected. Middle Graph: Calculated "potassium shift" associated with above response. Lower Record: Associated electrograms A to H, as marked on kymograph tracing above.

Figure 11 shows an example of effects ob-

* Concluding section of paper. Section I was published in this JOURNAL 2: 81, 1958.

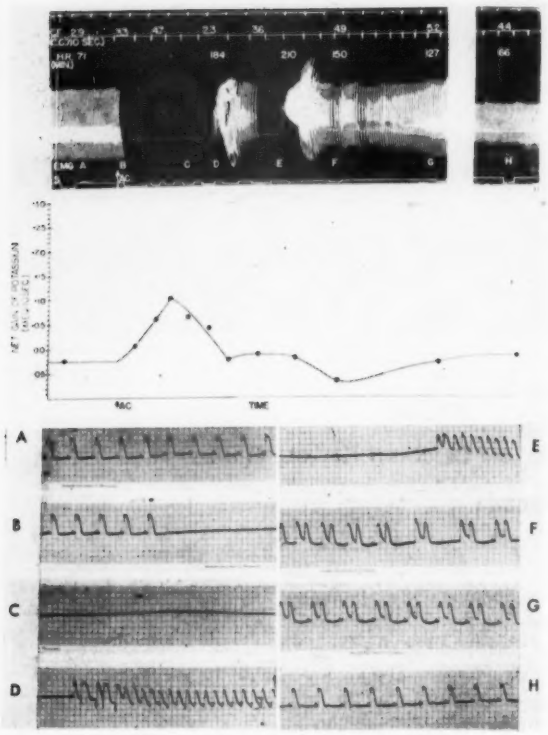

Fig. 11. Isolated rabbit heart perfused with Locke's solution containing 25 per cent of the normal potassium. (See legend, Fig. 2). Upper Record: At arrow, AC, 100 μg. of acetylcholine injected. Middle Graph: Calculated "potassium shift" associated with above response. Lower Record: Associated electrograms A to H, as marked on kymograph tracing above.

served when the perfusion fluid contained 25 per cent of the normal potassium content.

The injection (AC) of 100 μg of acetylcholine now induced immediate definite coronary dilatation, with temporary immediate cardiac arrest (40 sec). This was followed by an outburst of rapid and strong beats, succeeded in turn by a second period of complete arrest, again followed by rapid and irregular heart contractions. The heart activity returned to normal within 5 min. The middle graph shows that during this initial arrest there was a significant net gain of potassium by the heart, but on the contrary, there was some evidence of a slight increased net loss associated with the periods of cardiac stimulation. The concomitant changes in the electrograms taken at A to H are shown in the lower record. Immediately following the injection of acetylcholine, the complete absence of electrical activity with an occasional P wave is seen at B and C. At D, one sees this initial effect followed by a succession of irregular beats and sinus tachycardia (184 beats/min). A repetition of the effects is shown at E. Subsequently, the heart developed slow coupled beats, that is, each regular sinus

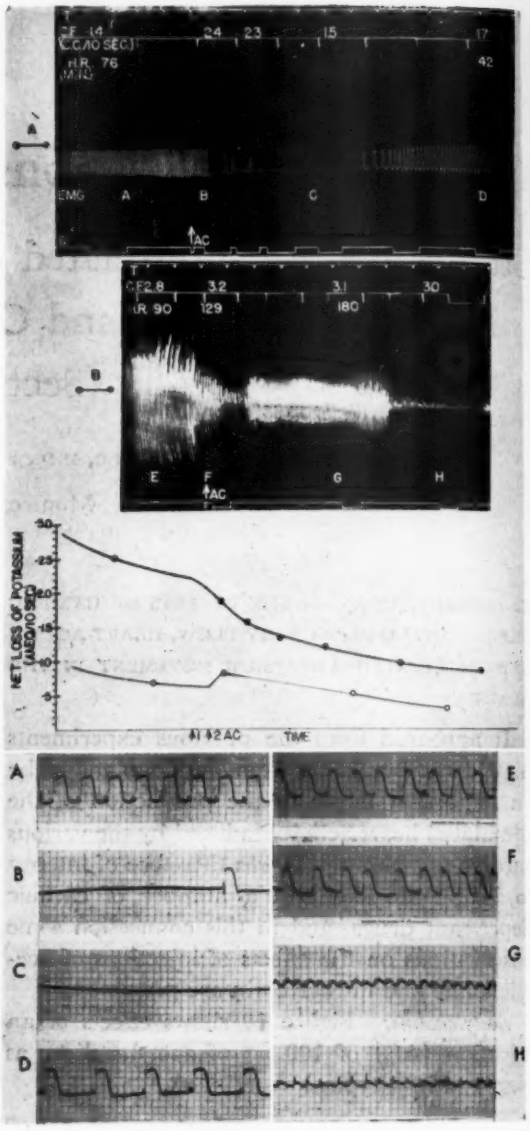

Fig. 12. Isolated rabbit heart perfused with potassium-free Locke's solution. (See legend, Fig. 2). Upper and Lower Kymograph Records are continuous. The upper tracing was started 2 min after an injection of KCl. At each arrow, AC, 100 μg of acetylcholine was injected. Middle Graph: Calculated "potassium shifts" associated with above response. Lower Record: Associated electrograms A to H, as marked on kymograph tracings above.

beat is followed by an ectopic beat (F and G) with final restoration to normal (H).

When the heart was perfused with potassium-free Locke's solution, as shown in the experiment reproduced in Figure 12, again temporary restoration of the potassium in the heart, followed

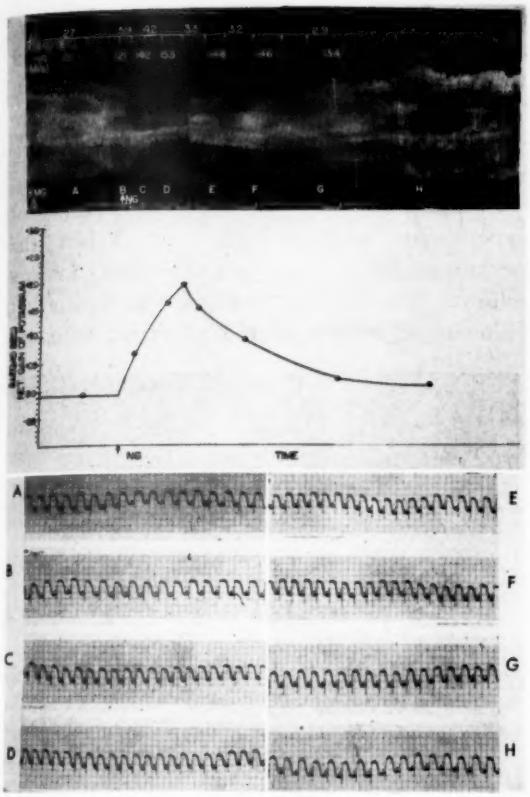

Figure 13. Isolated rabbit heart perfused with normal Locke's solution. Upper Record: At arrow, NG, 1 mg of nitroglycerin injected. Middle Graph: Calculated "potassium shift" associated with above response. Lower Record: Associated electrograms A to H, as marked on kymograph tracings above.

by acetylcholine (upper kymograph record), induced coronary dilation and instantaneous cardiac arrest lasting for 50 to 60 sec with occasional interspersed contractions. These were followed by a regular slow heart beat. However, when the potassium of the heart *was not restored*, as can be seen from the lower kymograph record, during the control period the amplitude and rate of the heart contractions were augmented, and following acetylcholine, there was a slight increase in coronary flow but *no inhibition of the heart contractions*, but rather irregular accelerated heart activity. Below the kymograph tracings are shown graphically the associated changes in potassium movement. As can be seen (closed circles), when the heart potassium is temporarily restored, there was a decrease in the existing net loss of potassium, while (open circles) when the heart potassium is not restored and injection of acetylcholine made, there was a slight increased "net loss" of potassium from the heart.

The concomitant electrograms (Fig. 12, lower record) obtained in these experiments as marked A to H, show that in the presence of "restored" cardiac potassium (A to D), there is the usual cardiac inhibition with occasional interspersed beats (B and C), but no evidence of A-V dissociation, and restoration to a slow sinus rhythm (D). However, when the potassium of the heart is depleted, during the control period (E), there was the unusual ventricular acceleration with A-V dissociation, and following acetylcholine there was a nodal tachycardia (F), and decreased voltage in all complexes with persistent tachycardia (G). Finally disordered ventricular activity of fibrillatory patterns with regular P waves (H) ensued. However, in none of these experiments was clear-cut ventricular fibrillation observed.

Nitroglycerin: Figures 13 and 14 show examples of the results obtained when nitroglycerin was injected during perfusion with normal Locke's solution on the one hand, and Locke's containing 25 per cent of the normal potassium on the other hand.

As can be seen (Fig. 13, upper kymograph record), following nitroglycerin (1 mg) there was the usual depression of the heart contractions, associated with the usual coronary acceleration. It is also evident that nitroglycerin like acetylcholine under these conditions leads to a "net gain" of potassium by the heart.

The lower section of Figure 13 also shows there is no significant change in the form of the electrogram after injection of the nitroglycerin. However, curiously enough, there was a slight temporary sinus acceleration from a control rate of 121 beats/min (A) to a maximum of 153 beats/min (D)—the rate returning to approximately normal (127 beats/min) within three min (H).

When the perfusion fluid was Locke's solution containing 50 per cent of normal potassium, the responses to nitroglycerin were rather similar to that shown above. However, following injection of nitroglycerin during perfusion with Locke's solution containing 25 per cent of the normal potassium, there was a striking prompt but *transient* coronary dilatation—the coronary flow rate increasing immediately from 3.1 cc to 8.1 cc per 10 sec (Fig. 14). It is, however, evident that under those conditions, there is only slight evidence of the usual depression of

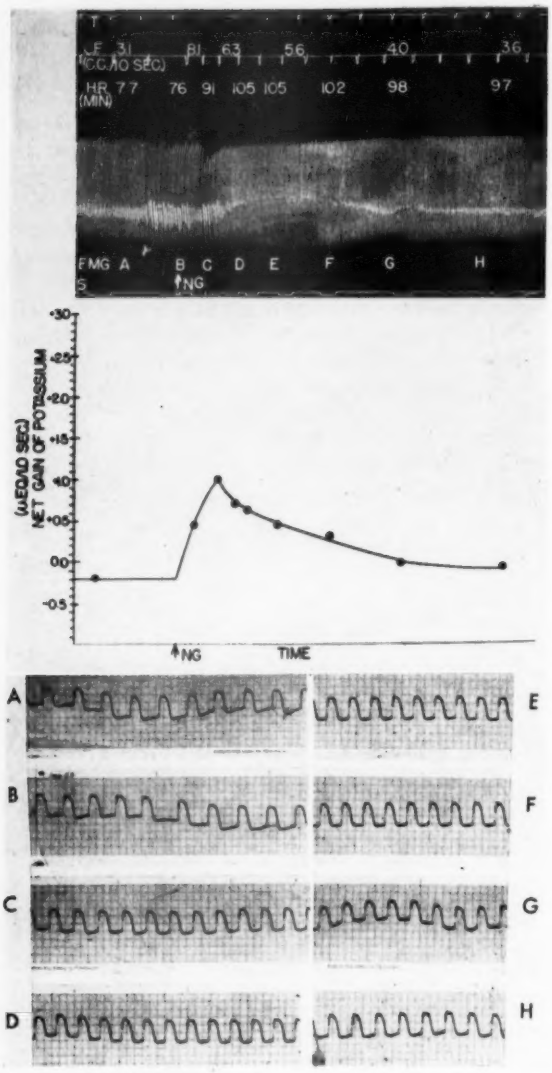

Fig. 14. Isolated rabbit heart perfused with Locke's solution containing 25 per cent of the normal potassium. Upper Record: At arrow, NG, 1 mg of nitroglycerin injected. Middle Graph: Calculated "potassium shift" associated with above response. Lower Record: Associated electrograms A to H, as marked on kymograph tracing above.

the heart contractions (compare Figure 13) following nitroglycerin. The middle graph shows that there was also an associated "net gain" of potassium under these conditions, but this was less marked than was observed during perfusion with normal Locke's solution.

The associated electrograms (A to H) showed no striking change in form throughout the postinjection period (B to H). There was however, a definite sinus tachycardia reaching a maximum of 105 beats/min (D), as compared with the control rate of 77 beats/min (A). This tachycardia also appeared to be more sustained than that observed with the drug during perfusion with normal Locke's solution.

Similar results were obtained in six different experiments with nitroglycerin. When the perfusing fluid was potassium-free Locke's solution, in other experiments it was shown that following injections of nitroglycerin, coronary

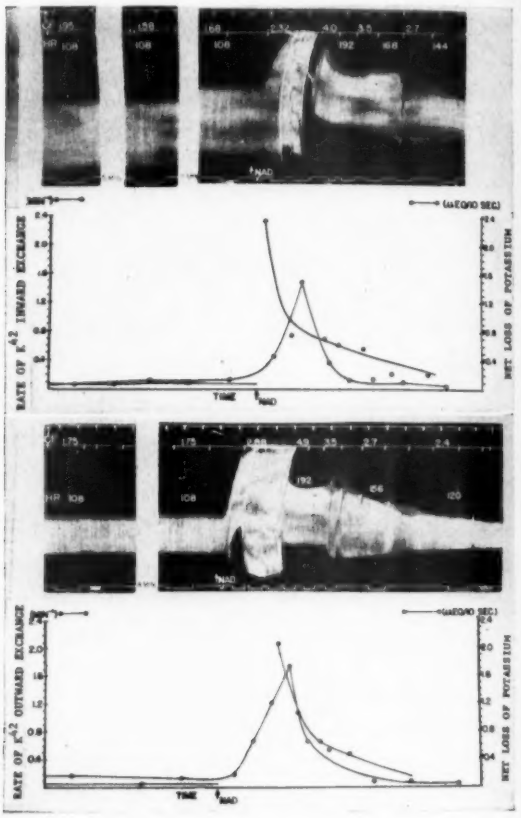

Fig. 15. Isolated rabbit heart perfusions (2 experiments). Experiment 1 (Upper Section): Normal Locke's solution with added K^{42}. Kymograph tracing (above) and graphs (below) showing calculated rates of inward exchange (K^{42}) with associated "net loss" of potassium (K^{39}). At arrow, NAD, 100 μg of norepinephrine was injected 17 minutes after perfusion was started. Experiment 2 (Lower Section) Normal Locke's solution. Kymograph tracing (above) and graphs (below) showing calculated rates of outward exchange (K^{42}) with associated "net loss" of potassium (K^{39}). At arrow, NAD, 100 μg of norepinephrine was injected 12 min after the perfusing fluid was changed from radioactive to nonradioactive Locke's solution. The records are similarly arranged in the succeeding figures.

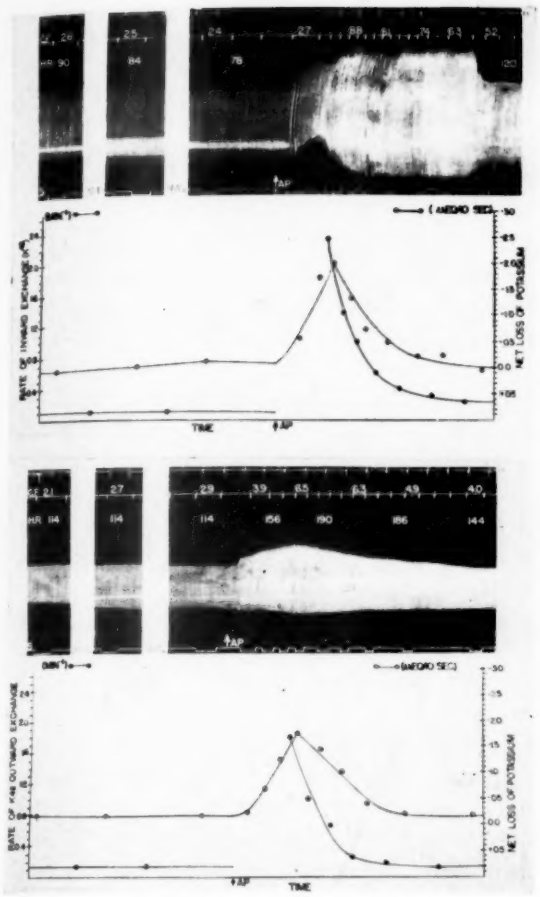

Fig. 16. Isolated rabbit heart perfusions (2 experiments). (See legend, Fig. 15). Exp. 1 (Upper Section): Normal Locke's solution with added K^{42}. At arrow AP, 5 mg of aminophylline was injected 15 min after the perfusion started. Graphs show inward exchange (K^{42}) and "net loss" (K^{39}). Exp. 2. (Lower Section): Normal Locke's solution. At arrow, AP, 5 mg of aminophylline was injected 10 min after the perfusing fluid was changed from radioactive to non-radioactive Locke's solution. Graphs show outward exchange (K^{42}) and "net loss" (K^{39}).

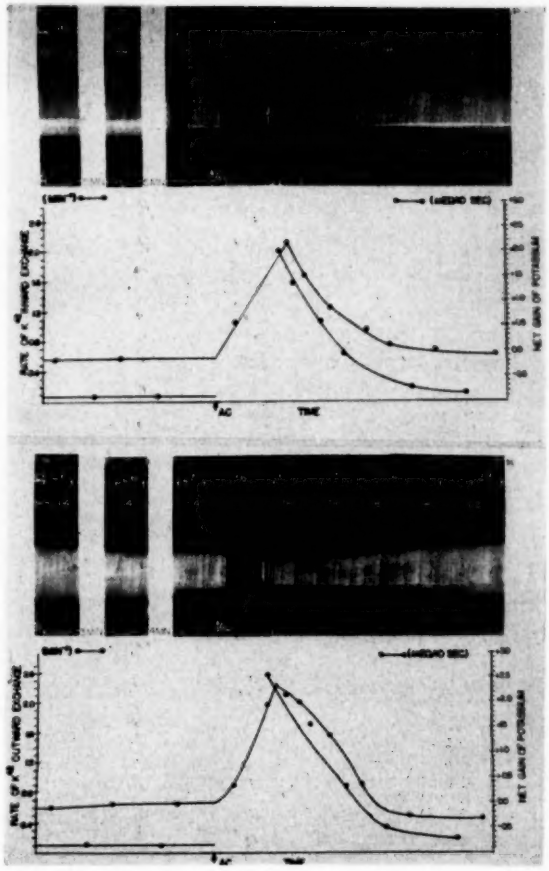

Fig. 17. Isolated rabbit heart perfusions (2 experiments). (See legend, Fig. 15). Exp. 1 (Upper Section): Normal Locke's solution with added K^{42}. At arrow, AC, 100 ug of acetylcholine was injected 15 minutes after perfusion started. Graphs show inward exchange (K^{42}) and net gain (K^{39}). Experiment 2. (Lower Section): Normal Locke's solution. At arrow, AC, 100 μg of acetylcholine was injected 10 min after the perfusing fluid was changed from radioactive to non-radioactive Locke's solution. Graphs show outward exchange (K^{42}) and net gain (K^{39}).

vasodilation and mechanical depression of the heart were still much less marked than with normal Locke, and the electrograms showed definite alterations (low voltage QRS and ventricular fibrillatory patterns).

III. Observations on the Effects of Cardiac Stimulants and Depressants upon Radioactive Potassium (K^{42}) Movement in the Heart

In this series of experiments the "inward" and "outward" exchanges of potassium as described earlier (Methods), were determined following similar injections of the various cardiac stimulants and depressants, as employed in the foregoing studies. In all of these experiments the perfusing fluid was normal Locke's solution, to which was added K^{42} as tracer. In a general way, the results obtained with all four cardiac stimulants (epinephrine, norepinephrine, isoproterenol, and aminophylline) were rather similar to those obtained with the two cardiac depressants (acetylcholine and nitroglycerin). Some typical examples of these results are shown in Figures 15, 16, 17, and 18,

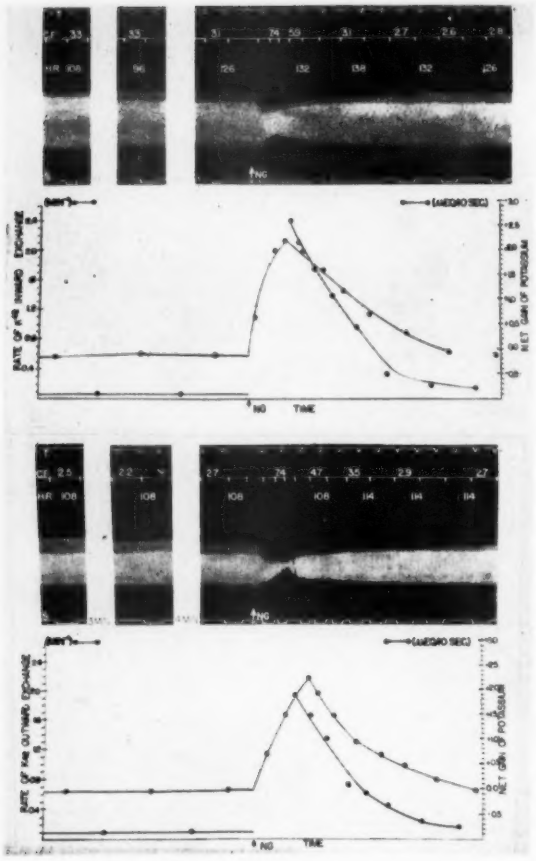

Fig. 18. Isolated rabbit heart perfusions (2 experiments). (See legend, Fig. 15). Experiment 1 (Upper Section): Normal Locke's solution with added K^{42}. At arrow NG, 1 mg of nitroglycerin was injected 15 min after perfusion started. Graphs show inward exchange (K^{42}) and net gain (K^{39}). Experiment 2 (Lower Section): Normal Locke's solution. At arrow, NG, 1 mg of nitroglycerin was injected 10 min after the perfusion was changed from radioactive to nonradioactive Locke's solution. Graphs show outward exchange (K^{42}) and net gain (K^{39}).

in which the effects of norepinephrine, aminophylline, acetylcholine, and nitroglycerin on both inward and outward exchanges were studied.

In regard to the changes in "*inward exchange*," as can be seen from the upper sections of the figures, during the preinjection periods, a relatively stable equilibrium was established, and the exchange rate was quite constant for 7 to 12 min. These records also show the associated coronary flow, heart contraction, and potassium (K^{39}) shifts, as previously referred to. These need no further comment, except to state that in every respect the findings agreed well with those already presented.

In each of the experiments shown, associated with these characteristic changes there was a prompt and striking increase in inward exchange rates. The average increased rates from three experiments with each agent were rather close, ranging from 20 to 24 times the control rates.

When the rate of K^{42} inward exchange is plotted on a positive scale (left ordinate), but the net change in K^{39} plotted as "net loss" (−) or "net gain" (+) (right ordinates), it is clear that the two sets of curves as obtained with the stimulant and the depressant drugs followed each other rather closely. In both instances there was also rapid return to the preinjection levels. It is therefore obvious that whether there is an associated "net loss" or "net gain" in the movement of K^{39}, there is a marked accelerated inward flux of potassium (K^{42}).

In regard to the changes in "*outward exchange*," as shown in the lower sections of each figure, again, the records show that in all experiments there is an accelerated rate of outward exchange. The maximum average changes after the cardiac stimulants were a 25-fold increase for adrenaline, a 42-fold increase for noradrenaline, a 22-fold increase for isoproterenol, and, a 13-fold increase for aminophylline. On the other hand, following injections of the cardiac depressants, the average outward exchange rate changes were 22-fold increases with both agents (acetylcholine and nitroglycerin). Similar findings have been observed in three experiments in which outward exchange rates were studied with each agent.

It is therefore clear that both the cardiac stimulants and the cardiac depressants accelerate the outward exchange of potassium. It is difficult with this technic to establish absolute quantitative differences between the degrees of inward or outward exchanges observed with the various agents, but correlating these findings with the over-all changes in potassium shift suggest strongly that the cardiac stimulants and cardiac depressants studied exert significant influences upon potassium exchange in the heart, which might conceivably trigger the mechanisms leading to either stimulation or depression of heart function.

Discussion

The results presented above clearly suggest that changes in heart action (stimulation or depression) as induced by the drugs studied, are related to changes in potassium shifts in the heart. It is, however, difficult from these data to establish definitely whether the latter are the cause or the effect of the former, and *vice versa*. The fact that the observed changes in potassium movement (net loss) associated with stimulation, and observed changes in potassium movement (net gain) associated with depression, vary inversely in the two groups of experiments would rather favor some direct or indirect relationship between the mechanical effects and the potassium alterations as observed under two sets of conditions. On the other hand, the rather similar degrees of change in both the inward and outward exchanges of radioactive potassium (K^{42}), whether the heart is stimulated or depressed, would suggest no such relationship between the mechanical effects and potassium alterations under the two sets of conditions. The possible significance of these anomalous observations will be discussed later.

In order that successive systole and diastole should occur in repetitive fashion in each cardiac cycle, it is imperative that "trigger mechanisms" involved be labile and rapidly reversible. Under the conditions employed in these experiments, changes in the "net potassium shifts" are the resultant of the sum total of potassium movement, as occurring both during the periods of contraction (systole) and the periods of relaxation (diastole) of the heart. The over-all effects might therefore be influenced to a considerable degree by changes in heart rate or in systolic/diastolic ratios associated with the effects of the agents studied. These special aspects of the problem have not been investigated in any detail so far, but some of the data present suggest tentative conclusions regarding their possible significances.

It is apparent from the extensive existing literature concerning the influence of potassium upon heart action, that "paradoxic" types of changes, i.e. both depression and stimulation, have been observed. This would rather indicate that the inward movements of this ion, that is, from the exterior or extracellular medium, as well as its outward movements, that is, from the interior or intracellular tissues of the heart, are highly variable and might depend upon the existing degree of saturation or desaturation of the heart with potassium. As already pointed out the heart is the most sensitive of all organs of the body to changes in potassium, and one of the main properties which differentiates potassium from other cations is its higher rate of mobility across cell membranes.[13]

Experimental Effects of Injections of Potassium on Heart Function

It has long been known that following injections of small doses of potassium in isolated rabbit heart prepartions, varying degrees of cardiac depression occur. However, following injections of high doses (exceeding 5 mg) of potassium chloride in the isolated rabbit heart perfused with normal Locke's solution, ventricular fibrillation ensues.[32] Wiggers has demonstrated clearly that electrical fibrillation of the ventricles of the dog's heart can be promptly stopped by large amounts (60 mg/kg) of potassium chloride. On the contrary, there are numerous studies in the literature to show that potassium salts injected intravenously in experimental animals can lead to ventricular fibrillation, and Wiggers[39] concludes from his studies on the question, that "doses of potassium smaller than those utilized to arrest fibrillatory contractions can produce in the normally beating heart a state resembling fibrillation, but not actually identical with it."

The characteristic electrical changes in the heart following injections of potassium have been described by numerous workers, employing both the isolated heart or the heart *in situ*. From the extensive studies of Hoff, Smith and Winkler,[19,40] these workers conclude that slow intravenous infusions of potassium in experimental animals induce widespread block in all parts of the heart associated with reduction in pacemaker automaticity. While following rapid infusions, the automaticity of the pacemaker is initially stimulated. It has been suggested that this latter action in the presence of the intraventricular block is responsible for the precipitation of the observed ventricular fibrillation. It is evident therefore, that the potassium ion might be in-

volved in physiological processes concerned with both excitation and depression of the heart function.

EXPERIMENTAL EFFECTS OF LOW POTASSIUM LEVELS ON HEART FUNCTION

Decreasing the potassium content in the perfusing fluids induces stimulation of the heart, and perfusion of the isolated rabbit heart with potassium-free Locke's solution leads rapidly to gross cardiac arrhythmias and ventricular fibrillation.[32] Indeed, the electrical changes observed during conditions of reduced potassium levels appear to be rather similar to those following injections of potassium, and characterized mainly by evidence of depression in conduction and increased ventricular excitability. Moreover, when the isolated papillary muscle of the cat is stimulated at constant rate, in a potassium-free Locke's solution, there is a repetitive response to each stimulus applied, but the *pattern of the electrical response remains unaltered.*[14] It is clear from these findings that the potassium induced changes in the electrical pattern of the heart when beating (either isolated or *in situ*) are not identical with those observed with isolated muscle strips. Some of the former changes might conceivably be only secondary.

CARDIAC POTASSIUM MOVEMENT AND THE EFFECTS OF DRUGS

Owing to the widespread distribution of potassium in body tissues and the high sensitivity of the heart to changes in serum potassium, it is difficult to assess the effects of drugs upon the movements of cardiac potassium with the heart beating *in situ*. In the previously published studies concerning the cardiac changes associated with alterations in serum potassium levels in both animals and man, various and contradictory types of electrical changes in the heart have been reported. This is doubtless due to the difficulty of evaluating to what extent such changes arise from secondary alterations in potassium shifts, that is, from potassium movement in extracardiac tissues, or from changes in the heart, that is, potassium movement in the heart *per se*.

In some studies, the changes (increase or decrease) in potassium content in the heart muscle have been determined following drug administration. The results obtained from this approach to the problem have also been rather contradictory. This is not surprising, since it is clear from the results described in this work that following injections of the various agents studied, gross changes in potassium (K^{39}) movements or in the radioactive potassium (K^{42}) exchanges, are exceedingly *transient*, and as already indicated, the measurable control rates of these shifts appear to be well restored despite the continued evidence of stimulation or depression of the heart functions.

It is however clear that when the potassium concentration in the perfusing fluid of the isolated heart is increased or decreased, the responses of the heart to various drugs can be significantly altered. Scarinci[35] has shown that following systolic arrest of the isolated frog heart by perfusion with normal Ringer's solution containing ouabain (1:30,000), changing the perfusing fluid to potassium-free Ringer's solution rapidly restores normal relaxation and contraction of the heart, which are maintained as long as the potassium-free Ringer's continues. Moreover, changing the perfusion fluid back to normal Ringer's solution rapidly throws the heart back into systolic arrest, showing that the ouabain was still acting. Thus, it was possible to show alternately normal activity and systolic arrest, by alternate short periods of perfusion with potassium-free Ringer's and normal Ringer's. It is evident, therefore, that the systolic effects of ouabain involve changes in cardiac potassium movements, and decreased extracellular potassium antagonizes ouabain action. This again is rather a paradoxic finding since, as is well-known, potassium injection has been claimed to diminish digitalis toxicity. It would appear from the above described findings, however, that the electrical changes induced in the beating heart by alterations in cardiac potassium movements (either primary or secondary) are *depression in conduction* and *increased irritability*, and these might be concerned with the antagonism to the digitalis action in the heart *in situ*. This problem needs further investigation.

As already emphasized, the changes in cardiac potassium shifts (net loss) following injections of the various cardiac stimulants (epinephrine,

norepinephrine, isoproterenol, and aminophylline) are rather similar. When the perfusing fluid is normal Locke's solution all of these agents induce almost exclusively a sinus tachycardia with no depression in A-V conduction, and no evidence of arrhythmias. On the other hand, during perfusion with the diminished concentrations of potassium, following injections of those agents there occurred invariably increasing degrees of A-V dissociation and block, associated with increasing degrees of ventricular hyperexcitability leading eventually to ventricular fibrillation.

Similarly, the changes in cardiac potassium shifts (net gain) following injections of the various cardiac depressants (acetylcholine and nitroglycerin) were somewhat alike. During perfusion with normal Locke's solution, however, nitroglycerin induced some pacemaker stimulation associated with depression of ventricular conduction. Both of these effects were somewhat lessened during perfusion of the heart with decreased potassium concentrations. Acetylcholine also induced pacemaker inhibition associated with depression of both conduction and excitability, but no fibrillation. However, during perfusion with Locke's containing only 25 per cent of the normal potassium content following acetylcholine administration there was no evidence of depression in A-V conduction but some slight increased ventricular irritability (coupled ectopic beats) and no fibrillation. It is also noteworthy that under these conditions, pacemaker stimulation also occurs. Finally, with potassium-free Locke's solution, acetylcholine produced depression in conduction and increased excitability leading to ventricular fibrillation. Since the earlier described electrical changes in the beating heart following either increased or decreased potassium were rather similar, the observed electrical changes induced by these agents might conceivably be due to the associated opposite types of changes in cardiac potassium exchange, as were observed.

The results presented would not indicate that changes in heart rate *per se* are responsible for the observed potassium shifts following injections of these agents. Indeed, in the case of isoproterenol the tachycardia was rather intense and sustained, yet the results obtained with this agent were not significantly different from those following either epinephrine, norepinephrine, or aminophylline.

The fact that the above-described potassium shifts were not sustained might be due to the rapid readjustment of normal potassium equilibrium in the hearts. This would appear to be essential for normal heart action and therefore quite understandable. Moreover, relatively normal heart function can be maintained during perfusion of the heart with only 50 per cent of the normal potassium for several hours, and even with 25 per cent good function is maintained for some time. Indeed, there was approximately the same degree of net loss of potassium associated with injection of all the stimulant drugs despite perfusion with these relatively low concentrations of potassium, *but arrhythmias could be detected only at the lower concentrations*. These observations would indicate that potassium equilibrium in the heart can be maintained even with significantly decreased concentrations of potassium in the perfusion fluid. The data would also suggest that ventricular arrhythmias result only when a "certain critical level" of potassium loss is reached.

The failure to demonstrate striking differences between the rates of inward and of outward exchanges of radioactive potassium (K^{42}) might therefore be due to the relatively rapid restoration of potassium equilibrium in the heart irrespective of whether the heart is gaining or losing potassium, as was observed following injections of both the cardiac stimulants and cardiac depressants.

These results do not establish completely the mechanism by means of which these changes in potassium movement lead to either stimulation or depression of heart function following drug administration. However, the results strongly suggest that the observed shifts in cardiac potassium might be *primarily* involved in these changes in heart function, and perhaps are concerned with changes in permeability of the myocardium resulting from the disturbed relationships between extracellular and intracellular potassium. The potassium shifts resulting from administration of these agents might therefore act as some type of "trigger mechanism."

Finally the possibility arises, as has been sug-

gested by several earlier workers, that the above described changes in heart action associated with potassium movement might be due to relative increases of calcium in the heart.[17] In view of earlier experiments performed in this laboratory[32] in which both epinephrine and norepinephrine were shown to induce definite cardiac stimulation (increased rate and amplitude of heart contractions) during perfusion of the isolated rabbit heart with calcium-free Locke's solution, this seems very unlikely.

The experimental findings presented leave little doubt that cardiac responses to drugs can be considerably modified by changes in extracellular potassium concentrations, and again emphasize the importance of a proper assessment of the patient's electrolyte balance in the course of cardiovascular drug therapy.

Summary

The correlated effects of drugs on coronary flow, heart actions (mechanical and electrical), and potassium movements in the isolated perfused heart (modified Langendorff technic), were investigated. The potassium movements were studied by comparing nonradioactive (K^{39}) potassium in the perfusing fluids entering the heart and the concentrations of these leaving the heart as collected at short intervals (5 to 10 sec) before and after injections of each drug. It was observed that there is a transient *net loss* and increased rate of potassium (K^{42}) turnover following injections of epinephrine, norepinephrine, isoproterenol, and aminophylline. Following injections of acetylcholine and nitroglycerin, there was, conversely, a *net gain* of potassium (K^{39}), but a similar increased rate of potassium (K^{42}) turnover. Characteristic electrical changes progressively leading to ventricular fibrillation were associated, in all cases, with increasing degrees of potassium disequilibrium.

It is concluded that under the influence of these agents the observed potassium disequilibrium might induce changes in myocardial permeability, which might possibly act as "trigger mechanisms" responsible for the observed stimulation or depression of heart function. These findings emphasize the importance of a proper assessment of the patient's electrolyte balance in the course of cardiovascular drug therapy.

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Reviews

Ebstein's Malformation*

Clinical Findings and Hemodynamic Alterations

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EBSTEIN[1] in 1866 described the first case of this entity, consisting essentially of congenital malformation of the tricuspid valve and displacement of the valve downward into the right ventricle. This divides the ventricle into a small distal portion which is the functioning right ventricle and a proximal portion which functions as part of the right atrium. Yater and Shapiro[2] in 1937 reviewed the literature, found 15 previously reported cases and added another case of their own. They did not think that this entity could be positively diagnosed during life. In 1950 Engle *et al.*[3] reported three cases, bringing the total number to 26 cases. They analyzed the clinical aspects of this disease and predicted that there were sufficient characteristic features to allow the clinical diagnosis. Reynolds[4] and Soloff *et al.*[5] reported the first cases diagnosed during life. With the widespread use of modern diagnostic methods, such as catheterization and angiocardiography, and a better understanding of the clinical syndrome, a considerable number of cases have recently appeared in the literature, diagnosed clinically. Medd *et al.*[6] in 1954 reviewed the 26 cases since 1948 and added another case. They further delineated the diagnostic criterion for this disease. Recently Kilby *et al.*[7] have presented an excellent review of the literature with a summary of previous cases and an evaluation of the findings. They were able to find 71 previously reported cases and added five cases of their own. Four other cases have been reported.[8] More recently Blount and co-workers discussed the hemodynamic findings in four cases in more detail.[9]

PATHOPHYSIOLOGIC ASPECTS

The basic defect in Ebstein's disease is displacement of the tricuspid valve downward into the right ventricle with malformation of the valve leaflets. The right ventricle is divided into a small distal portion which is the functioning right ventricle, and the portion above the valve which functions as part of the atrial chamber. There may be a varying amount of displacement of the valves but the functioning right ventricle is usually greatly diminished in size. The wall of the atrial portion of the right ventricle is very thin. The ventricular portion is usually of normal thickness. The malformation of the leaflets is variable and often they are so fused and deformed that it is difficult to differentiate the individual leaflets. Sometimes they are only bands of fibrous tissue. The anterior leaflet is usually the largest and is partially attached to the annulus fibrosus. The posterior and medial cusps arise from the wall of the right ventricle and interventricular septum. The posterior leaflet is frequently the most deformed. The posterior cusp may be fused to the ventricular endocardium. The medial cusp is frequently a functionless flap and the anterior cusp may form a sheet-like structure.

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There is much variation in the anomalous chordae tendinae and papillary muscles, which are usually poorly developed. The Eustachian and Thebesian valves are frequently well-developed. There may be only a malformation of normally inserting valves[10] and there is a variable degree of valvular displacement. The right atrium is enlarged and hypertrophied. There is frequently an associated patent foramen ovale. Kilby *et al.*[7] in reviewing the literature found 41 autopsied cases of which 35 had a patent foramen ovale. In 30 living cases there was clinical evidence of patent foramen ovale in all but six cases.

At postmortem study the malformed valve may sometimes appear to have been competent and sometimes was obviously incompetent. Clinical signs of tricuspid insufficiency are rare. This may be due to the small ejection volume of the right ventricle, buffering action of the large volume of the functioning right atrium, and overflow through the patent foramen ovale.[2,8] At times there appears to have been a functional tricuspid stenosis.[3,7] Increased pressure in the right atrium leads to right to left shunt when there is a patent foramen ovale. There is a close correlation between the presence of cyanosis and patent foramen ovale.

Clinical Aspects

Dyspnea is a very common complaint in Ebstein's syndrome. Symptoms may be minimal or absent and the syndrome may be compatible with a long life. Walton and Spencer's[11] patient lived to the age of 53 and did not have symptoms until one year before death. Physical and mental development is usually quite good. Dyspnea and palpitation may be precipitated by paroxysmal tachycardia which has often been reported in these patients. Recently, Brown *et al.*[8] found this in two out of four patients and considered it very characteristic of Ebstein's disease. Cyanosis is very common and is well correlated with atrial septal defect, as has been stated before. Kilby *et al.*[7] in their recent survey of the literature found this in 84 per cent of the cases and absent in 16 per cent where mention was made of this symptom. Its appearance may be considerably delayed. Clubbing may or may not be present. Medd *et al.*[6] have stressed a decrease or absence of the thrust to the left of the sternum which is often found in other cases of right ventricular hypertrophy, as a diagnostic point.

A systolic murmur is usually present and often associated with a diastolic murmur. Less often, a diastolic murmur is present alone. The systolic murmur is usually loud and rough, but may often be faint.[10] It is maximal in the 3rd and 4th interspaces at the left sternal border or in the lower precordial area. The diastolic murmur is usually in the lower precordial areas.[10] There may be associated thrills. Kilby *et al.*[7] found eight patients in the literature with no murmur and they also had one patient of their own who did not have any murmurs. A frequent auscultatory sign which has been given considerable diagnostic significance is the presence of a triple or gallop rhythm.[6,8,10] This is usually heard in the area of the 4th left interspace near the sternum and is early diastolic in time. Kilby *et al.*[7] found this sign in 24 instances in the literature and in four of their five new cases. Brown *et al.*[8] found this in all four of their cases. The first heart sound may also be split. As mentioned previously, signs of tricuspid insufficiency are rare.

Electrocardiogram

The electrocardiogram may be of diagnostic aid in Ebstein's disease. Gøtzsche and Falholt,[10] in a review of 16 cases in the literature, found no case with a normal electrocardiogram. The most characteristic finding is right bundle branch block. This is usually of an atypical form, the most common being a low voltage R wave with marked splintering of the R′ deflection in V_1.[7] Michel *et al.*[12] describe a pattern in the limb leads 2 and 3 consisting of a normal looking R followed by a broad wave similar to an atrial wave ending in an elevated ST segment. They attribute this late wave to the delayed activation of the atrial portion of the right ventricle. Prominent peaked P waves are commonly found and occasionally increased A-V conduction time is present. Sodi-Pallares and Marsico[13] have recently emphasized the occurrence of Wolff-Parkinson-White syndrome as characteristic enough to make one consider Ebstein's disease in a patient with con-

TABLE I
Catheterization Findings in Three Cases of Ebstein's Anomaly

		PA	RV	RA	LA	PVC	SVC	IVC	BA
Case 1	Pressures	23/12	43/8	12/6	—	8/3	—	—	130/70
	O_2 content, volume %	13.2	—	13.4	—	—	13.4	—	17.9
	O_2 saturation %	73	—	75	—	—	75	—	100
	Cardiac output	2.8 *l*/min							
	Cardiac index	2.5 *l*/min/m²BS							
Case 2	Pressures	15/6	20/8	10/5	10/2	10/2	—	—	100/70
	O_2 content, volume %	15.3	15.2	15.5	18.2	—	13.6	15.4	18.2
	O_2 saturation %	76	75	78	91	—	68	77	91
	Cardiac output								
	Systemic	5.2 *l*/min							
	Pulmonary	4.2 *l*/min							
	Cardiac index	2.8 *l*/min/m²BS							
	L to R shunt	1.0 *l*/min							
Case 3	Pressures	18/8	24/5	10/3	—	8/2	—	—	110/60
	O_2 content, volume %	13.3	14.0	13.6	—	—	12.1	13.7	17.4
	O_2 saturation	74	78	76	—	—	67	76	97
	Cardiac output	5.0 *l*/min							
	Cardiac index	3.0 *l*/min/m²BS							

genital heart disease. The tendency for paroxysmal tachycardias has already been referred to. Conduction disturbances are particularly prone to occur during catheterization.

X-RAY

In Ebstein's disease there is marked cardiac enlargement both to the right and to the left. There is prominence on the right due to the large right atrium and a long convex left heart border without prominence of the pulmonary conus region. This gives the heart a globular appearance. There is normal to decreased vascularity of the lungs. A frequent observation has been decreased pulsations over the right ventricle and pulmonary artery.[3,8,10] The aorta frequently appears narrow. In the lateral view there is marked increase in contiguity of the anterior surface of the heart with the anterior wall of the thorax.[14]

ANGIOCARDIOGRAPHY

Angiocardiography presents a rather characteristic picture in Ebstein's syndrome. The angiocardiographic diagnosis was recently emphasized by Kistin *et al.*[15] The right atrium is found to be greatly enlarged with delayed emptying of the right atrium and the right ventricle. Soloff *et al.*[5] and Kistin *et al.* were both able to demonstrate a notch or band separating the functioning right ventricle from the auricular portion of the right ventricle. This is considered pathognomonic. There is poor or absent visualization of the pulmonary arteries. A right to left interatrial shunt may be demonstrated. Kjellberg *et al.*[14] have emphasized the dangers of angiocardiography in this condition.

CARDIAC CATHETERIZATION

The catheterization findings are often diagnostic in Ebstein's disease. The most important diagnostic feature is the finding of the large right atrium with an abnormally placed tricuspid valve. It is noted that the change from atrial pressure to ventricular pressure is displaced far to the left. It is often difficult or impossible to pass the tricuspid valve, the catheter coiling up in the enormous right atrium. The right atrial pressure is usually elevated, but may be normal. The pressures are normal in the right ventricle and pulmonary artery. An atrial

pressure tracing indicating tricuspid insufficiency is seldom found. Kilby *et al.*[7] found four such cases in the literature and considered the finding present in two of the nine cases found at the Mayo Clinic. Kjellberg *et al.*[14] considered the atrial pressure curve of tricuspid insufficiency to be present in all four of their cases. In two cases of Kilby *et al.*[7] no gross abnormality in the position of the tricuspid valve could be demonstrated. As mentioned previously, an interatrial septal defect is often found by direct catheterization of a defect or evidence of a right to left shunt.

Blount *et al.*[9] discussing the hemodynamics in Ebstein's anomaly, described as typical a broad and delayed right ventricular pressure curve and a late diastolic wave in both the right ventricular and pulmonary artery pressure tracings. The former was attributed to a delayed activation of the right ventricle, the latter to transmission of a forceful atrial pulse which may participate in the propagation of the blood into the pulmonary artery.

A mild pressure gradient between the systolic pressures of the right ventricle and pulmonary artery was frequently described. Blount and co-workers attributed this to a hypoplastic pulmonic valve-ring and pulmonary artery. True valvular pulmonic stenosis was not found in postmortem examinations.

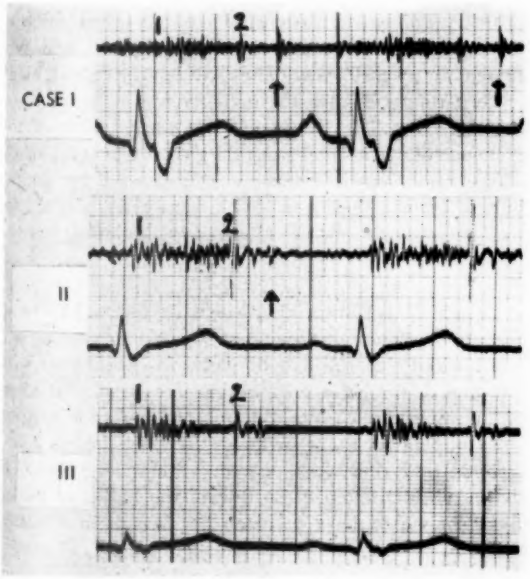

Fig. 1. Phonocardiograms taken in the 4th left intercostal space near sternum. Note 3rd heart sound in case 1 and 2 (arrow).

Case Reports

The purpose of this report is to discuss some of the hemodynamic changes and clinical findings based on three of our cases diagnosed in life by cardiac catheterization, and, in one case, by angiocardiography also. The symptoms and clinical findings of the three cases, a 14-year-old boy, a 17- and a 13-year-old-girl, are summarized as follows:

Case 10. This 14-year-old boy had a history of collapse lasting several minutes at the age of three. At that time a murmur was first noticed. Subsequently, the development of the child was relatively good and uneventful. At the age of 13 following excessive exercise, severe shortness of breath and dizziness occurred which lasted several hours. His exercise tolerance had become decreased and he became more easily fatigued than his playmates.

Physical examination revealed a 14-year-old boy who was small for his age and was without cyanosis. A grade II to III systolic murmur was present at the base of the heart and the 4th left interspace near the sternum. There was some transmission to the neck area. There was a reduplication of the 2nd heart sound at the 4th left interspace near the sternum, giving a marked triple rhythm. (Fig. 1.) X-ray examination revealed a globular shaped heart, enlarged to both the right and to the left. The lungs showed decreased vascular markings. There was a small aorta. In the electrocardiogram there was normal sinus rhythm with prominent and peaked P waves in leads 2, 3, aVF, and the right-sided chest leads. There was a right bundle branch block with splintering of the R′ in 3 and V_1. R′ was tall in V_2 and V_3. (Fig. 2.)

Right heart catheterization showed a normal pulmonary artery pressure with some gradient between the right ventricular and pulmonary artery systolic pressures. The point of change from a ventricular to a right atrial pressure pattern was markedly displaced to the left side of the heart during withdrawal of the catheter on several occasions. An x-ray taken with the tip of the catheter still in the right atrium showed this displacement of the tricuspid valve to the left and a small right ventricle. The right atrial pressure was slightly elevated with a prominent A-wave. There was no indication in the tracing of tricuspid insufficiency. The pulmonary capillary wedge pressure was lower than the right atrial pressure. There was no evidence of left to right or right to left shunt. The cardiac output was rather low. The dye curve from the right atrium to the ear showed a delayed appearance time and a prolonged return to the baseline. The analysis of the right ventricular pressure tracing revealed a slight delay (0.10 sec) between the beginning of the QRS and the onset

of the rising pressure. The pulmonary artery pressure rose slowly to a late peak with an anacrotic notch. There was a late diastolic elevation in the right ventricular and pulmonary artery pressure tracings.

The interesting feature in this catheterization was that while the catheter was in the right ventricle, the bundle branch block disappeared for a short period without interruption of the normal sinus rhythm. The right ventricular pressure tracing was markedly different when the electrocardiogram showed normal intraventricular conduction than when it showed bundle branch block. The onset of the ventricular pressure rise came at the normal time and the peak was reached very fast, as in a normal pressure tracing. After removing the catheter from the right ventricle the bundle branch block pattern recurred without change in the normal sequence of the sinus rhythm. This occurred twice during catheterization, each time when the catheter was in the right ventricle. (Fig. 3.)

CASE 2. This 17-year-old white female had a known heart murmur since the age of four. She was restricted in her activities by the family physician. However, she seemed to be able to keep up with the other children. At the time of admission she denied exertional dyspnea or fatigue. She also did not have palpitation or irregular heart beat. The patient looked somewhat pale and there was a questionable blue tinge of the lips. There was a loud blowing systolic murmur in the 3rd and 4th intercostal spaces just to the left of the sternum. A third heart sound was audible in the 5th left intercostal space near the sternum, producing a triple rhythm. The x-ray showed a slight increase of the transverse diameter of the heart and in the lateral position increased contiguity of the right ventricle with the sternum. The lungs showed normal vascularity. However, the left and right pulmonary arteries were rather small. The electrocardiogram revealed a horizontal electrical position and an incomplete right bundle branch block pattern. There was a rather prominent P wave in 2, V_5 and aVF.

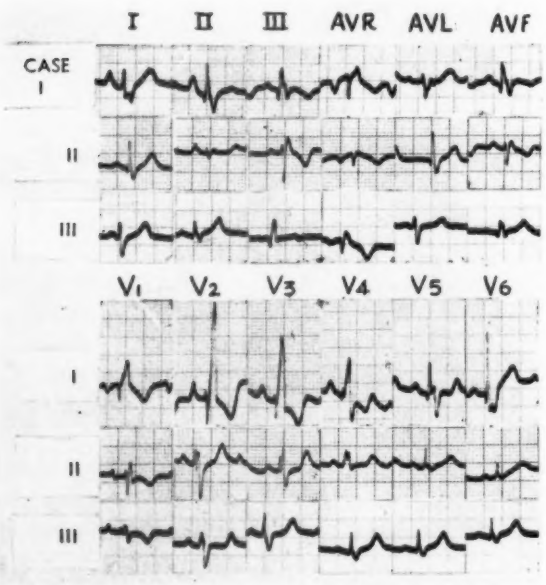

Fig. 2. Electrocardiograms of the three reported cases.

The cardiac catheterization indicated a normal pulmonary artery pressure and a slight gradient across the pulmonic valve. The right atrial pressure was slightly elevated and showed a prominent A-wave. On withdrawal of the catheter from the right ventricle to the right atrium, the pressure tracing showed displacement of the tricuspid valve to the left side of the heart. The catheter could be passed through a patent foramen ovale to the left atrium. The left atrial pressure was lower than the right and also showed a prominent A-wave. There was no evidence of left to right shunt. However, there was a mild oxygen desaturation in the left atrium and in the brachial artery. The right to left shunt was verified by dye injection curves from the right atrium, showing an early dip. The pulmonary flow was within normal limits and there was a 25 per cent right to left shunt. (Table I.)

An angiocardiogram had been performed elsewhere which showed marked dilation of the right atrium and delayed emptying of this chamber. The right ventricle and the pulmonary artery were filled slowly and with low dye concentration.

The pressure tracing from the right ventricle showed a normal onset and a similar delay of the peak as in the previous case. There was also a marked elevation of the late diastolic pressure. This patient, during catheterization of the right ventricle, developed an ECG pattern similar to Wolff-Parkinson-White syndrome. This pattern occurred without interruption of the normal sequence of the sinus rhythm and was present for several beats. The right bundle branch block pattern returned after the catheter was removed from the right ventricle, again without interruption of the sequence of the normal sinus rhythm. The comparison of the right ventricular pressure tracings during right bundle branch block and WPW syndrome showed that the time of onset was not changed in the latter, but the peak was reached much faster. (Fig. 4.)

CASE 3. This 13-year-old obese white girl had Osgood-Schlatter's disease at the age of five. Since that time it was noticed that she had difficulty in keeping up with children of similar age. She became tired and short of breath more easily. Six months before admission she complained about dizzy spells which lasted a few seconds and then disappeared. She had periods of dyspnea which often came during the night, at which times she would have to catch her breath in a sitting position. She had had intermittent chest pains of a few minutes' duration for a year, not related to exertion. There was no history of edema, cough, or palpitation.

There was no evidence of cyanosis. A harsh low-pitched grade III systolic murmur was heard over the

entire precordium. The murmur was loudest in the fourth left intercostal space beside the sternum. There was no evidence of a diastolic murmur. There was a reduplication of the second sound in the 4th left intercostal space. The x-ray showed a normal transverse cardiac diameter, and no definite selective cardiac enlargement could be detected. The lung fields appeared to be normal. The electrocardiogram showed an incomplete right bundle branch block pattern and a vertical position.

Cardiac catheterization indicated a normal pulmonary artery pressure and a slight systolic pressure gradient across the pulmonic valve. During cardiac catheterization displacement of the tricuspid valve to the left was noted on several occasions when the catheter was withdrawn from the right ventricle. The right atrial pressure was slightly elevated and showed a marked A-wave. The pulmonary capillary wedge pressure, on the other hand, was normal. There was no evidence of intracardiac shunts and the brachial artery blood was normally saturated. The cardiac output was within normal limits. The circulation dye curves showed a slight delay of the dye appearance time and a rather late return to the baseline. The right ventricular pressure tracing showed no delay of the onset, but there was slight delay in reaching the peak. There was also some elevation of the end-diastolic pressure.

This patient developed a wandering pacemaker between the sinus and A-V node during catheterization while the catheter was in the right ventricle. The incomplete right bundle branch block pattern persisted during this period. The shape of the right ventricular pressure curve did not change during the period of wandering pacemaker. During the nodal beats, with P waves buried in the QRS complex, the end-diastolic pressure elevation could not be seen. However, at the time of the ventricular pressure peak there was a superimposed wave possibly indicating simultaneous contraction of the right atrium and right ventricle with superimposed pressure wave on the right ventricular pressure tracing.

Fig. 3. Right ventricular and right atrial pressure tracings in case 1. Note the delayed onset and peak of the right ventricular pressure tracing when the electrocardiogram shows right bundle branch block and the absence of it during normal conduction. (Paper speed 25 mm/sec.)

Discussion

Ebstein's disease was suspected only in the first case before cardiac catheterization. The suspicion was based on the presence of a triple rhythm, the characteristic globular-shaped heart on the x-ray film and the atypical right bundle branch block. It seemed that this case was the most typical among the three and the degree of displacement of the tricuspid valve was probably the most marked. On the other hand, no patent foramen ovale with right to left shunt could be detected. In case 2 there was a right to left shunt. This patient had no symptoms. It is possible that the escape mechanism through the patent foramen ovale was responsible for this. The smaller right atrium in this case might be attributed to this factor.

The malformation was present in its mildest form in the 3rd case. The symptoms in this patient were partly psychogenic. However, some impairment of the right ventricular ejective force was indicated by the delay of the pressure peak.

As previously mentioned, Ebstein's anomaly is found to occur in different degrees from mild malformation to marked displacement of the tricuspid valve. While the mild forms produce no symptoms on normal daily activity, cardiac

reserve is probably decreased even in these patients and a tendency to cardiac arrhythmias may be present.

In case 1 there was a complete right bundle branch block pattern while in cases 2 and 3 it was incomplete. This difference possibly represents the degree of physiologic stress imposed on the right ventricle and correlates with severity of the displacement of the tricuspid valve and the dilatation of the atrial portion of the right ventricle. It was suggested that the block is not an intrinsic element of the anomaly caused by a defect in the conduction system itself, but is the result of the dilatation and strain of the atrialized portion of the right ventricle.[9]

how the intraventricular conduction defect could disappear on stimulation of the right ventricle or atrium by the catheter and how this can change the shape and contour of the ventricular pressure tracing, including the disappearance of the delay of onset and peak. Two explanations might be suggested:

(1) Michel *et al.*[12] believe that the late wave in the ECG (P′) is a manifestation of the electrical activation of the atrial portion of the ventricle. It might be suggested that the disappearance of the prolonged intraventricular conduction is due to partial blocking of the electrical activation of the ventricle, especially of the atrial portion. The pressure peak in the

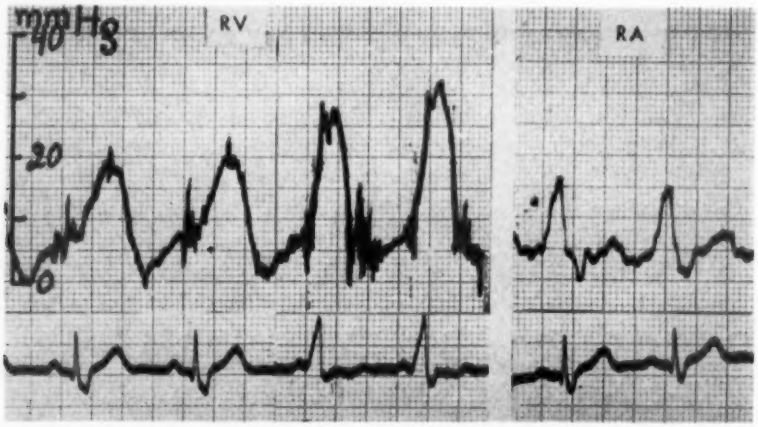

Fig. 4. Right ventricular and right atrial pressure tracings in case 2. Note delayed right ventricular pressure rise during right bundle branch block and normal rise during WPW syndrome. (Paper speed 25 mm/sec.)

Pathogenesis of Conduction Disturbances: In right bundle branch block there is an increased delay between the onset of the QRS complex and right ventricular contraction, as recently again emphasized by Braunwald *et al.*[16] A delay of the onset of the right ventricular pressure rise was present in case 1, while in cases 2 and 3 the onset was within normal limits. In the first case this may be attributed to complete right bundle branch block. The fact that during the apparently normal intraventricular conduction caused by the catheter in the ventricle the time of onset of the ventricular pressure was earlier than during prolonged conduction, would speak for a true conduction disturbance in the latter. It is difficult to explain

right ventricle was markedly delayed during bundle branch block, while there was no delay of the peak during normal conduction. It is possible that the electrical activation as well as the mechanical contraction of the anatomically abnormal portion of the right ventricle is delayed, while the functioning portion of the right ventricle is normally activated. This, however, would not explain the difference in the onset of activation. Furthermore, the blocking of the atrial portion of the right ventricle would probably not affect the right ventricular pressure tracing because this portion probably does not participate in the right ventricular ejection.

(2) An alternative explanation for the disappearance of the prolonged intraventricular

conduction in this case may be given by the findings of Lev and co-workers.[17] They found, besides atypical A-V conduction tissue, unusually located conduction fibers in the septum running from left to right in a case of Ebstein's malformation with Wolff-Parkinson-White syndrome. Such aberrant conduction fibers from left to right across the septum may not be unusual in Ebstein's malformation. It is possible that in Ebstein's malformation with complete right bundle branch block the right ventricular activation occurs by such aberrant conduction pathways through the septum rather than through the normal pathway. The catheter could have blocked the pathways in our case with the activation occurring through the shorter normal conduction pathway. The latter explanation appears to be more plausible than the former because it would explain both the earlier onset and peak of the right ventricular pressure pattern.

Pre-excitation syndrome in Ebstein's disease is not uncommon. Some patients sometimes show persistent Wolff-Parkinson-White syndrome. In the 2nd case, the pre-excitation developed on stimulation of the ventricular wall by the catheter. This would support the findings of Lev *et al.*[17] of aberrant A-V pathway and the assumption that blocking of normal pathways through interference by the catheter can lead to A-V conduction by such aberrant pathways if present. The ventricular pressure curve with a broad and delayed peak changed to a normal pressure contour during pre-excitation of the ventricle. This delay of the peak and the presence of normal contour during pre-excitation could not be an artifact because the changes occurred consistently with the changes in ventricular activation. Pre-excitation might occur in other cardiac diseases during cardiac catheterization. We did not find a single instance in reviewing our more than 300 cardiac catheterizations. We believe that in Ebstein's anomaly there is often an abnormality of the right ventricular conduction system which is responsible for the delayed activation and altered right ventricular dynamics. Furthermore, it would help to explain the frequent tendency to arrhythmias.

Right Ventricular Contraction: The angiocardiography performed in case 2 in a slight left anterior oblique position showed the typical features for Ebstein's disease of a markedly enlarged right atrium and considerable delay of the dye in this chamber with late and insufficient filling of the pulmonary artery. The films revealed during atrial contraction a distinct border between the atrium proper and the atrialized portion of the right ventricle. This could be seen as an indentation between the lower and mid-portion of this enlarged chamber. During atrial diastole this indentation disappeared. It seemed that the right atrium proper contracted vigorously, while there was no indication of contraction in the atrialized portion of the right ventricle. If contraction of the atrialized portion would take place, it should be during ventricular systole. Since this part of the right ventricle is very thin-walled, no hemodynamically effective contraction can be expected. On the other hand, the atrial contraction is so forceful that the pressure wave is transmitted to the right ventricular and even pulmonary artery pressure tracings as a late diastolic wave. Blount and co-workers[9] believe that the atrial contraction possibly plays a role in the propagation of the blood to the pulmonary arteries. Thus, in Ebstein's anomaly there is a forcefully contracting right atrium proper and a small part of the right ventricle which performs the ventricular ejection. Between the two is the atrialized ventricular chamber not performing any useful action. This mechanism could be seen quite well in the angiocardiogram of this patient. The narrow band of contrast medium described by Soloff and co-workers as the tricuspid valve leaf could not be seen because the pictures were not taken in the right anterior oblique position. (Fig. 5.)

Summary

Clinical, electrocardiographic, cardiac catheterization and angiocardiographic findings in Ebstein's malformation of the tricuspid valve were reviewed. Three of our own cases are reported, showing different degrees of the malformation and different degrees of symptoms, from impaired cardiac function, to almost no reduction of cardiac efficiency. Ebstein's malformation may be suspected and diagnosed

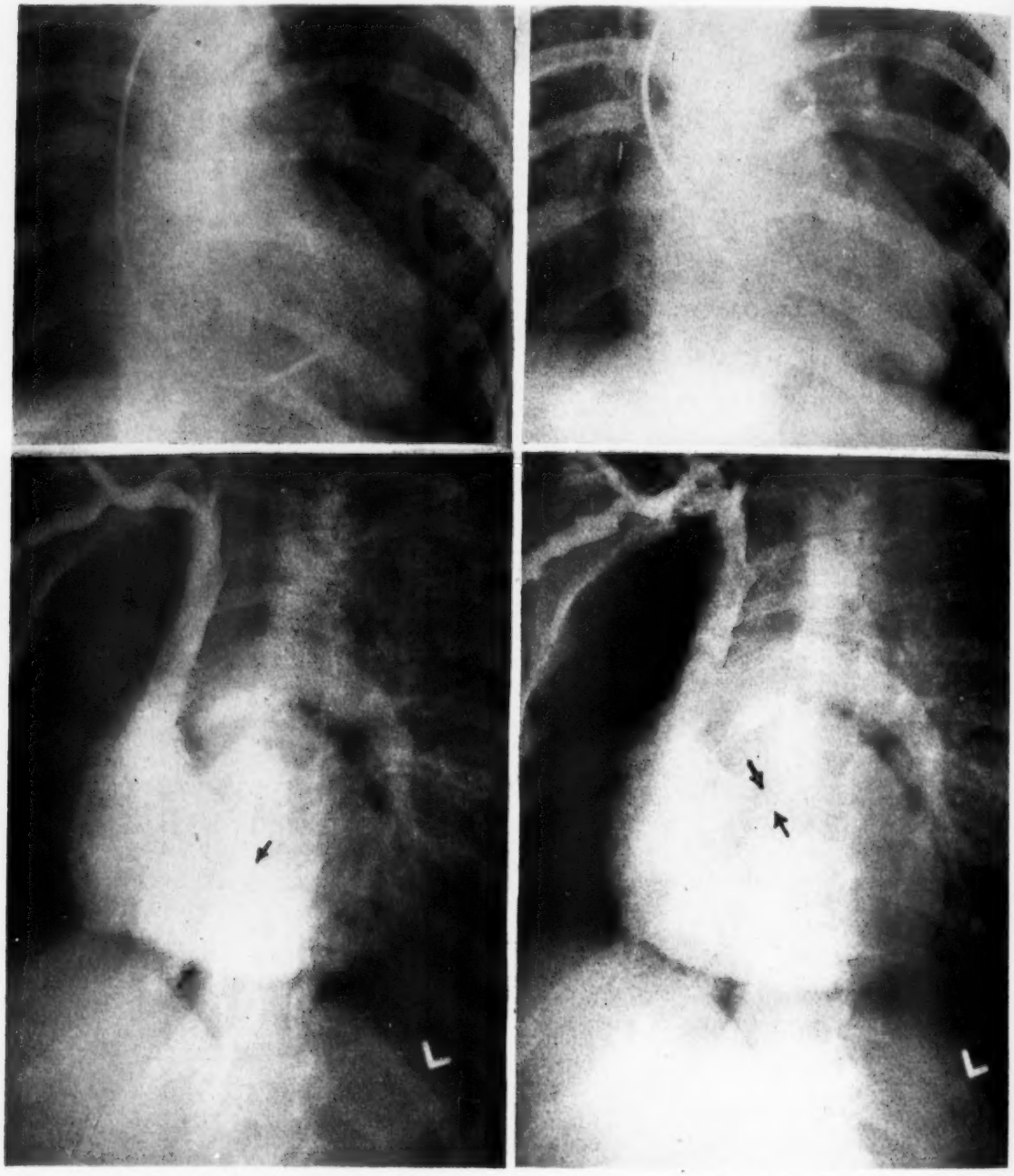

Fig. 5. Angiocardiography (lower two pictures) in case 2. The upper left picture indicates catheter tip still in right atrium while lower left picture shows enlarged right atrium filled with dye. Between arrows is the probable normal atrioventricular border. Right upper picture shows catheter through patent foramen ovale in the left atrium. Lower right picture shows right to left shunt in same location (between arrows).

clinically. However, in some cases the degree of malformation is mild and the findings are less typical clinically. Cardiac catheterization usually leads to the diagnosis.

An unusual normalization of the previous right bundle branch block pattern occurred in one of the cases during cardiac catheterization, which lasted for 20 to 25 cardiac cycles and appeared and disappeared without any change in the normal sinus rhythm. The previous

delay in the onset of the right ventricular pressures and the broadening and late peak disappeared during the normal conduction. Two possible alternative explanations are offered which might shed some light on the electrical activation and hemodynamics of the right ventricle in Ebstein's malformation. It is possible that the catheter blocked the activation of the atrialized portion of the right ventricle and thus changed the right ventricular hemodynamics. On the other hand, it is possible that aberrant right ventricular conduction mechanism is present in Ebstein's malformation which changed to a shorter and normal intraventricular conduction when interference from the catheter blocked the aberrant pathways. Such aberrant pathways are supported by the occurrence of right ventricular pre-excitation in another case during cardiac catheterization.

Angiocardiography in one of the patients showed that in Ebstein's malformation there is a hemodynamically non-functioning part of the right atrium, the atrialized portion of the right ventricle, which is placed between the vigorously contracting right atrium and the functioning small part of the right ventricle.

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Ebstein's Anomaly*

Complete Review of 108 Cases

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WILHELM EBSTEIN in the year 1866 described a peculiar anomaly of the tricuspid value in a 19-year-old cyanotic youth who had a history of palpitations and died with clinical manifestations of tricuspid regurgitation.[1] At autopsy the anterior and posterior leaflets of the tricuspid valve were fused and placed abnormally low, bulging out into the right ventricle. The septal leaflet was rudimentary and the foramen ovale was patent.

It was a full 20 years before a similar case of Ebstein's anomaly of the tricuspid valve was reported.[2] After 60 years only 14 additional cases had been added to the original.[3–11] In 1937 Yater and Shapiro[12] reported the first case with roentgenologic and electrocardiographic studies. These authors concluded that this condition could not be diagnosed during life. However, in 1950 Engle[13] concluded that Ebstein's anomaly produced a clinical syndrome sufficiently characteristic to be correctly diagnosed although, to their knowledge, this had not been accomplished as yet. But in the previous year Tourniaire, Deyrieux, and Tartulier[14] had already made the diagnosis of Ebstein's anomaly with the aid of cardiac catheterization during the lifetime on the patient. Since then many cases have been diagnosed through the use of cardiac catheterization and angiocardiography in addition to those found at autopsy.[15–53, 62–70]

We are reporting three new cases diagnosed during life, in addition to giving a complete review of the literature on Ebstein's anomaly, consisting of 108 cases in all.

CASE HISTORIES

CASE 1. J. R., male, age 14, entered St. Louis City Hospital on December 16, 1954 with the complaints of cyanosis, tiredness, and shortness of breath on moderate exertion throughout his life. Physical examination showed a blood pressure of 125/90, pulse 92, and respirations 22. No clubbing or cyanosis was present at rest. The lung fields were clear. The heart was enlarged to the left anterior axillary line.

During the auscultatory and phonocardiographic study, the heart had a normal sinus rhythm with a rate varying between 62 and 79 beats per minute. The first heart sound was not audible in any area although it occasionally made a minimal deflection on the oscilloscope at the apex and tricuspid areas (Fig. 1A). The pulmonic second sound was normal and the aortic second sound was decreased in intensity. Throughout systole and heard all over the precordium was a single harsh, diamond-shaped systolic murmur. This was loudest (grade 4/6) between the fourth intercostal space just to the left of the sternum and the tricuspid area; however it was also quite loud at the cardiac apex.

Diastole was clear except for the presence of two extra heart tones. Early in diastole, occurring 0.16 sec after the second heart tone, was a high-pitched, snapping, extra heart tone, loudest at the apex, tricuspid area, and up to the lower portion of the left sternal border. This was similar in quality to the usual opening snap heard in mitral stenosis. The second extra heart sound was of very low pitch and was heard in the latter part of diastole, loudest at the tricuspid area. This occurred 0.12 sec after the onset of the P wave on the electrocardiogram, and 0.11 sec before the first heart sound deflection.

The electrocardiogram (Fig. 2) showed sinus tachycardia at a rate of 110 with a P-R interval of 0.16 sec.

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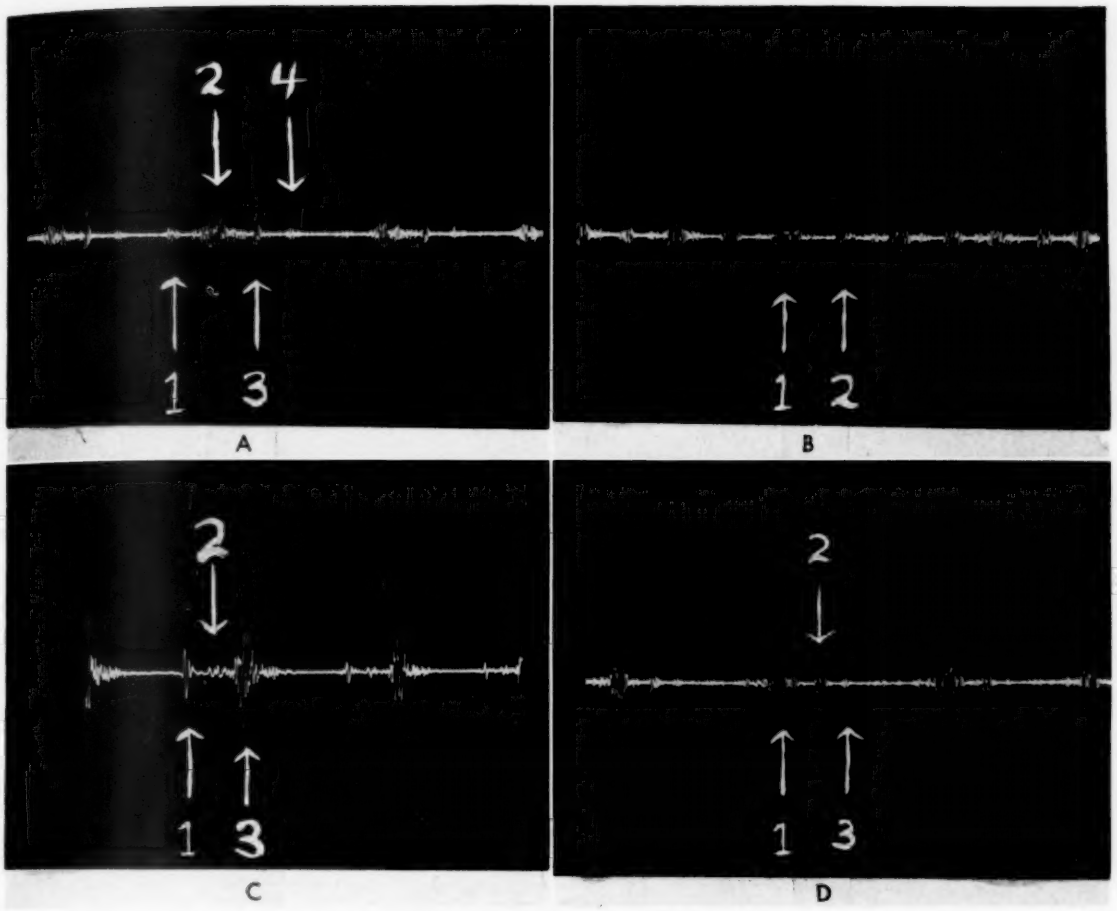

Fig. 1. Photographs (using Polaroid Camera) of oscilloscopic projections of tape recordings of heart sounds on Cambridge Electron-cardioscope. The timing of these phenomena was proved by simultaneous electrocardiography. (A.) Case 1. Tricuspid area. (1) Low pitched extra heart sound in late diastole occurring at the bottom of downstroke of P wave. (2) Diamond-shaped grade IV systolic murmur. (3) Approximately normal second heart sound. (4) Early diastolic snapping extra heart sound. The first sound is not audible nor visible. Heart rate 71 per min. (B.) Case 2. Tricuspid area. First and second heart sounds are neither audible nor visible. (1) Diamond-shaped grade IV systolic murmur. (2) Somewhat low pitched extra heart sound occurring at the bottom of the downstroke of the P wave. Heart rate 113 per min. (C.) Case 3. Cardiac apex. (1) Low pitched extra heart sound occurring on downstroke of the P wave. (2) First heart sound not audible but there are minimal deflections on oscilloscopic screen. The second heart sound and the early diastolic extra heart sound are not heard in this area. (3) Diamond-shaped grade IV systolic murmur which has the same intensity at tricuspid area. Heart rate 85 per min. (D.) Case 3. Pulmonic area. (1) Same murmur as in C but less intense here. First sound again not audible. (2) Second heart sound much diminished from the normal. (3) Early diastolic snapping extra sound. No recording made at mid-left sternal border. Heart rate 85 per min.

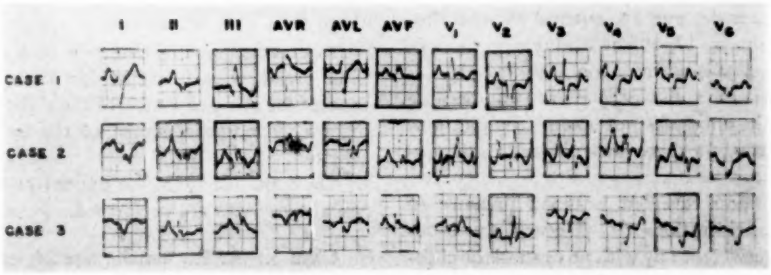

Fig. 2. Electrocardiographic tracings made on the three new cases.

The QRS was widened to 0.11 sec and was notched or slurred in all leads. The P waves were abnormally tall and there was right axis deviation in the standard leads. The unipolar limb leads revealed an indeterminate electrical position. In the precordial leads V_{1-3} an rSR's' with an intrinsicoid deflection of 0.07 sec was present. Interpretation was incomplete right bundle branch block, atrial pathology, and myocardial change and/or digitalis effect.

Fluoroscopy and roentgenography revealed an enlarged heart of globular shape, the enlargement being predominantly right auricular, and apparently right ventricular. Pulmonary vascularity was diminished. The aortic shadow was small and no left auricular enlargement was noted (Fig. 3).

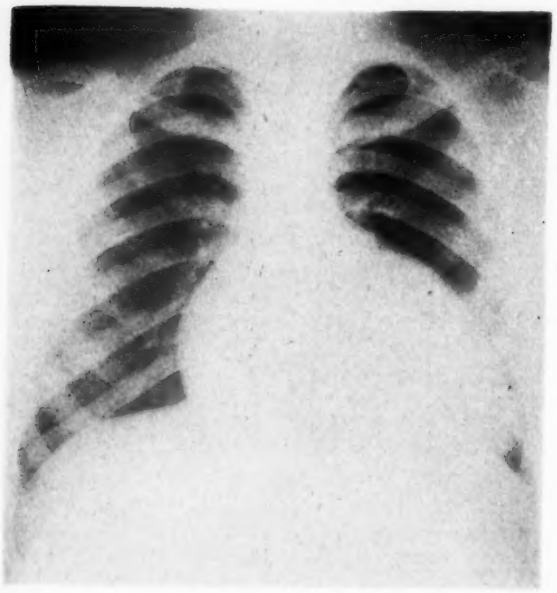

Fig. 3. Roentgenogram of the chest in case 1.

Cardiac catheterization revealed no intracardiac shunt. The arterial oxygen saturation was normal at rest but dropped to 82 per cent with exercise. Pressures were elevated in the right auricle and normal in the right ventricle and pulmonary artery. The characteristic course of the catheter (to be discussed later) was elicited (Fig. 7).

Case 2. R. W., male, age 14, entered Firmin Desloge Hospital on January 17, 1954 with the complaint of having had shortness of breath for many years, with increase in severity during the past year. He became moderately cyanotic only after exertion. Palpitations occurred on exertion but there was no history of paroxysmal tachycardia.

Physical examination revealed a blood pressure of 108/82, pulse 108, respirations 20. He was a well-developed, slightly overweight boy with no cyanosis or clubbing. Lung fields were clear. Jugular pulsations were visible. The heart was enlarged to the left anterior axillary line and to the right of the sternum.

During the period of auscultation and phonocardiographic study the heart rate ranged between 109–115 per minute (Fig. 1B). The diminished first heart sound was loudest at the left sternal border between the 4th intercostal space and the pulmonic area. It was not heard at the apex or tricuspid areas although a minimal deflection was made on the oscilloscope in these areas. The second heart sound had a diminished intensity at the base. It was louder at the aortic than at the pulmonic area.

Throughout systole there was a diamond-shaped, rather harsh murmur which was loudest (grade 4) between the 3rd and 4th intercostal spaces just to the left of the sternum, but was heard all over the precordium. Diastole contained a low-pitched heart sound which occurred constantly in mid-diastole. The first deflections of this extra sound on the oscilloscopic screen occurred 0.12 sec after the onset of the P wave and was 0.08 sec in duration. This is longer in duration than is usually found in extra heart tones, although an occasional protodiastolic gallop makes a tone of similar duration. This diastolic extra heart sound was loudest between the 3rd and 4th intercostal space just to the left of the sternum and was quite well heard at the tricuspid area and apex. This sound may well represent a summation of two extra sounds, which were discretely heard in diastole in the other two cases.

The electrocardiogram (Fig. 2) showed sinus tachycardia at a rate varying between 120 and 130 per min. The P-R interval was 0.18 sec (predicted for age and rate 0.16 sec). The QRS was widened to 0.16 sec and notched or slurred in all leads. The standard leads showed right axis deviation and the P waves were of abnormal form and high amplitude. In the precordial leads over the right ventricle a qrsR′ pattern was noted with an intrinsicoid deflection of 0.11 sec in V_1. Interpretation was complete right bundle branch block, atrial pathology, first degree heart block, a myocardial change and/or digitalis effect.

Fluoroscopy and roentgenography revealed an enlarged heart of globular shape with a relatively narrow aortic silhouette. The right auricular segment was particularly large. The pulmonary conus-artery segment was relatively concave and pulmonary vascularity was diminished (Fig. 4).

Cardiac catheterization revealed no left to right shunting of blood within the heart. Ear oximetry showed a drop from 95 to 85 per cent in arterial oxygen saturation with exercise, giving evidence of a right to left shunt. The pressures on the right side of the heart were normal except for some elevation of the right auricular pressure. The characteristic course of the cardiac catheter was elicited.

On Sept. 12, 1955, the patient had a sudden demise; an autopsy was not performed.

Case 3. A. R., female, age 24, entered Firmin Desloge Hospital on June 1, 1955 with complaints of short-

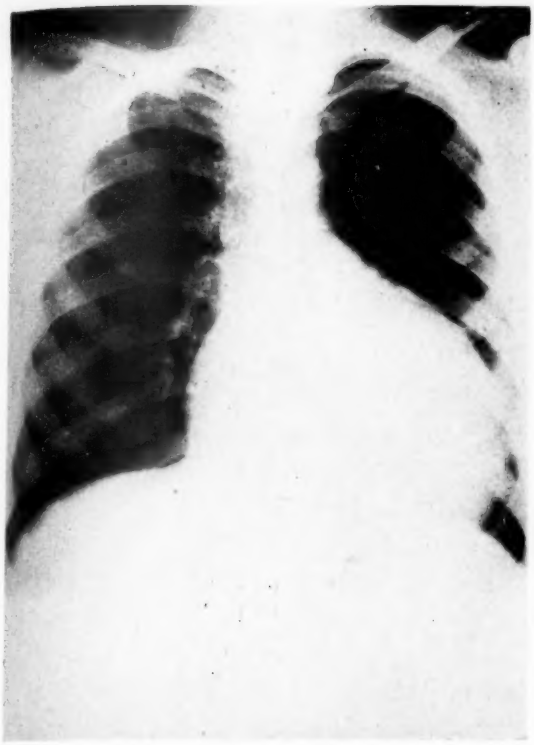

Fig. 4. Roentgenogram of the chest in case 2.

ness of breath and a heart murmur diagnosed when she was six years of age. Frequent bouts of fainting and paroxysmal tachycardia were also reported. No history of heart failure was elicited. Cold weather caused her nose and lips to become cyanotic, otherwise no history of cyanosis was elicited.

Physical examination revealed a blood pressure of 106/64, pulse 80, respirations 16. The patient was well developed and not cyanotic. Lung fields were clear. Heart examination revealed enlargement of the heart to the left anterior axillary line.

Auscultation (heart rate varying between 85–90) revealed that the first sound was not audible in any area although at the apex and tricuspid areas it made a minimal deflection on the oscilloscope. A diminished second heart sound was slightly louder at the pulmonic than at the aortic area (Fig. 1C). A harsh, diamond-shaped murmur was present throughout systole and was heard all over the precordium. This was loudest (grade 4) and equally present between the cardiac apex and tricuspid areas.

Diastole was clear of murmur but contained two extra heart sounds. In early diastole, along the left sternal border, occurring 0.11 sec after the second heart sound was a single, high-pitched, extra heart sound. This resembled the usual opening snap of the mitral valve in mitral stenosis. The second extra heart sound occurred late in diastole and was loudest at and just inside the cardiac apex. This was a very low-pitched tone and occurred 0.14 sec prior to the first heart sound deflection, at the end of the downstroke of the P wave of the electrocardiogram.

The electrocardiographic tracing (Fig. 2) revealed sinus rhythm at a rate of 70 per min. The P-R interval was 0.16 sec, the QRS interval was 0.16 sec and the complexes were widened or slurred in all leads. The standard leads showed right axis deviation and the P waves were abnormal in shape. The unipolar leads showed an indeterminate electrical position. Over the right precordium a qrSR′ complex was recorded with the intrinsicoid deflection prolonged to 0.10 sec in V_1. The interpretation was complete right bundle branch block, possible atrial pathology and myocardial change.

Fluoroscopy and roentgenography revealed the heart to be markedly enlarged and globular with particular enlargement of the right auricular segment. The aortic shadow was relatively inconspicuous. Vascularity of the lung field was diminished (Fig. 5).

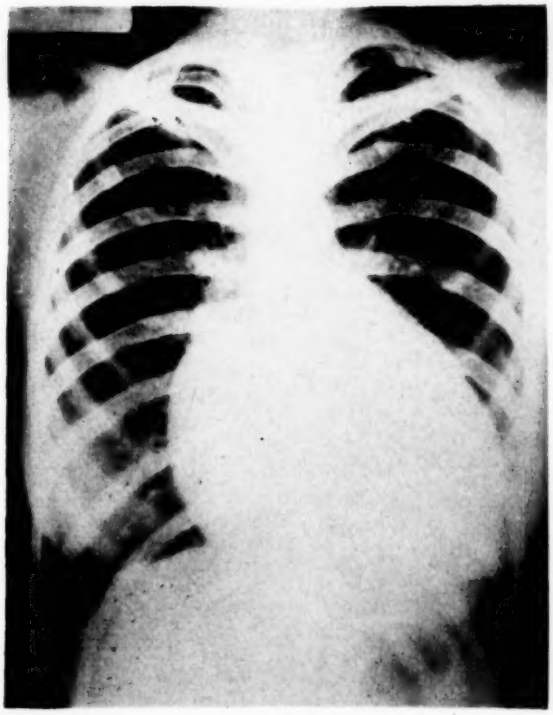

Fig. 5. Roentgenogram of the chest in case 3.

Cardiac catheterization revealed no intracardiac shunt. The arterial oxygen saturation was normal at rest and after exercise. Intermittent tachycardia during the test caused considerable rise in auricular pressure. There was also evidence of tricuspid regurgitation from the pressure tracing. The right ventricular and pulmonary artery pressures were normal. A large arteriovenous oxygen difference indicated a lowered cardiac output. The characteristic course of the catheter through the right auricle and ventricle was seen.

TABLE I

Reported Cases of Ebstein's Anomaly

Case	Year	Author	Age	Sex	Cyanosis	Shunt	ECG	X-ray	Cardiac catheterization	Diagnosis during life	Remarks
1	1866	Ebstein	19	M	Yes	PFO	No	No	No	No	Tuberculosis
2	1886	Marxsen	61	F	?	PFO	No	No	No	No	—
3	1900	McCallum	30	M	Yes	PFO	No	No	No	No	Tuberculosis
4	1903	Shonenberger	4½	F	Yes	PFO	No	No	No	No	Sudden death
5	1903	Geipel	18	M	?	PFO	No	No	No	No	Museum specimen
6	1903	"	?	?	?	PFO	No	No	No	No	Museum specimen
7	1903	"	15	M	Yes	PFO	No	No	No	No	Paradoxical embolus
8	1908	Malon	60	M	?	?	No	No	No	No	—
9	1913	Heigel	10	F	Yes	PFO	No	No	No	No	Cerebral abscess
10	1913	"	3	F	Yes	PFO	No	No	No	No	—
11	1913	"	38	F	?	No	No	No	No	No	Museum specimen
12	1919	Morison	38	M	Yes	No	No	No	No	No	Tuberculosis
13	1922	"	33	M	No	No	No	No	No	No	Sudden death
14	1927	Arnstein	20	F	Yes	PFO	No	No	No	No	Tuberculosis
15	1928	Abbott	16	M	Yes	PFO	No	No	No	No	—
16	1937	Yater	21	F	Yes	PFO	Yes	Yes	No	No	Sudden death
17	1937	Zink	19	M	Yes	PFO	No	No	No	No	Tuberculosis
18	1939	Obiditsch	46	M	Yes	PFO	No	No	No	No	Sudden death
19	1945	Brekke	8 mo	F	Yes	PFO	No	Yes	No	No	—
20	1945	Bauer	27	F	Yes	PFO	Yes	Yes	No	No	Sudden death
21	1947	Berber	?	?	?	?	Yes	?	No	No	Fetal endocarditis?
22	1947	Taussig	18	M	Yes	PFO	Yes	Yes	No	No	—
23	1948	Walton	53	F	Yes	PFO	Yes	Yes	No	No	Paradoxical embolus
24	1949	Tourniaire	39	F	No	?	Yes	Yes	Yes	Yes	Calcified valve?
25	1950	Engle	10	F	Yes	PFO	Yes	Yes	No	No	—
26	1950	"	5	M	Yes	PFO	Yes	Yes	Yes	No	Blalock-Taussig operation, died
27	1950	"	16	F	Yes	PFO	Yes	Yes	No	No	Blalock-Taussig operation, died
28	1950	Baker	17	M	Yes	PFO; ASD	Yes	Yes	Yes	No	Sudden death after catheterization
29	1950	"	11	F	Yes	PFO; ASD	Yes	Yes	Yes	No	Died after exploration
30	1950	Hueck	7	F	Yes	PFO	No	Yes	No	No	—
31	1950	Reynolds	33	F	Yes	ASD*	Yes	Yes	Yes	Yes	—
32	1951	Barger	30	M	No	PFO; ASD	Yes	Yes	No	No	Brain abscess
33	1951	Paul	16	M	?	No	Yes	No	No	No	—
34	1951	Soloff	34	F	No	ASD†	Yes	Yes	No	Yes	—
35	1951	"	2 da	M	?	?	No	No	No	No	—
36	1951	Groux	72	M	No	No	Yes	Yes	No	No	—
37	1951	Schaede	9	F	Yes	PFO	Yes	Yes	Yes	No	Died suddenly after angiocardiogram
38	1951	"	15	M	Yes	?	Yes	Yes	No	No	Sudden death
39	1951	Mannheimer	3	F	Yes	?	Yes	Yes	Yes	Yes	—
40	1952	Van Linden	22	F	Yes	ASD*	Yes	Yes	Yes	Yes	—
41	1952	"	20	F	Yes	ASD*	Yes	Yes	Yes	Yes	—
42	1952	Blacket	16	F	Yes	No*	Yes	Yes	Yes	Yes	—
43	1952	"	2½	M	No	PFO	Yes	Yes	No	No	Sudden death after catheterization

TABLE I (*Continued*)
Reported Cases of Ebstein's Anomaly

Case	Year	Author	Age	Sex	Cyanosis	Shunt	ECG	X-Ray	Cardiac catheterization	Diagnosis during life	Remarks
44	1952	Deglaude	20	M	Yes	?	Yes	Yes	?	?	—
45	1952	Blacket	18	F	Yes	PFO†	Yes	Yes	No	Yes	—
46	1952	"	13	M	Yes	?	Yes	Yes	No	Yes	—
47	1952	"	13	M	Yes	?	Yes	Yes	No	Yes	—
48	1952	Grob	5	F	Yes	ASD*	Yes	Yes	Yes	Yes	—
49	1953	Goodwin	14	M	Yes	PFO; ASD	Yes	Yes	No	Yes	Blalock shunt operation, died
50	1953	"	13	M	Yes	ASD*	Yes	Yes	Yes	Yes	—
51	1953	Gasul	2 wk	F	Yes	PFO; ASD	Yes	Yes	No	No	Died after exploration
52	1953	"	16 mo	F	Yes	ASD	Yes	Yes	Yes	No	Died after Potts-Smith
53	1953	Broadbent	6	M	Yes	PFO; ASD	Yes	Yes	Yes	No	Died after exploration
54	1953	"	35	M	Yes	ASD*	Yes	Yes	Yes	Yes	—
55	1953	"	29	M	Yes	ASD*	Yes	Yes	Yes	Yes	—
56	1953	Henderson	26	M	Yes	ASD*	Yes	Yes	Yes	Yes	—
57	1953	Edwards	2 mo	?	?	ASD	?	?	?	No	—
58	1953	"	2 mo	?	?	VSD	?	?	?	No	—
59	1953	Nocker	26	M	Yes	PFO	Yes	Yes	No	No	Sudden death
60	1954	Gotzche	10	F	Yes	ASD*	Yes	Yes	Yes	Yes	—
61	1954	"	7	F	Yes	ASD*	Yes	Yes	Yes	Yes	—
62	1954	"	17	M	Yes	ASD*	Yes	Yes	Yes	Yes	—
63	1954	"	26	M	No	No*	Yes	Yes	Yes	Yes	—
64	1954	"	22	M	No	No*	Yes	Yes	Yes	Yes	—
65	1954	"	21	M	Yes	ASD*	Yes	Yes	Yes	Yes	—
66	1954	Medd	6½	F	Yes	ASD*	Yes	Yes	Yes	Yes	—
67	1954	Wright	26	M	Yes	PFO‡	Yes	Yes	Yes	Yes	Surgical closure of defect
68	1954	Cisneros	8	F	Yes	PFO‡	Yes	Yes	Yes	Yes	Heart explored
69	1954	Heim de Balsac	24	M	Yes	PFO	Yes	Yes	?	Yes	Sudden death: autopsy
70	1954	"	9	M	?	?	Yes	Yes	?	Yes	—
71	1954	"	23	M	Yes	?	Yes	Yes	?	Yes	—
72	1954	"	8	F	Yes	?	Yes	Yes	?	Yes	—
73	1954	Gotshalk	22	M	Yes	PFO	Yes	Yes	No	No	Brain abscess
74	1954	Kirchmair	27	M	No	No	Yes	Yes	No	No	Cardiac arrest after sympathectomy
75	1954	Bayer	21	F	Yes	ASD*	Yes	Yes	Yes	Yes	Hypertension
76	1954	"	24	F	Yes	ASD*	Yes	Yes	Yes	Yes	—
77	1954	"	10	M	Yes	ASD*	Yes	Yes	Yes	Yes	—
78	1954	Bernard	55	F	Yes	ASD	Yes	?	Yes	Yes	—
79	1955	Kerwin	18	M	Yes	No	Yes	Yes	Yes	Yes	Sudden death
80	1955	Lev	2	M	Yes	PFO	Yes	Yes	No	No	Potts-Smith operation, died
81	1955	Lenegre	65	M	Yes	PFO	Yes	Yes	Yes	No	—
82	1955	"	18	M	Yes	PFO	Yes	Yes	No	No	Antero-septal fibrosis; mural fibrosis
83	1955	"	15	F	Yes	ASD*?	Yes	Yes	Yes	Yes	—
84	1955	"	4½	M	Yes	ASD*	Yes	Yes	Yes	Yes	—

Table I is continued on p. 216

TABLE I (*Continued*)
Reported Cases of Ebstein's Anomaly

Case	Year	Author	Age	Sex	Cyanosis	Shunt	ECG	X-Ray	Cardiac catheterization	Diagnosis during life	Remarks
85	1955	C.P.C.[48]	45	F	Yes	PFO	Yes	Yes	Yes	Yes	PFO closed surgically, died
86	1955	Zak	30	M	Yes	PFO	Yes	Yes	No	No	Parodoxical embolus
87	1955	Kistin	26	M	No	No‡	Yes	Yes	Yes	Yes	Diagnosis by angio
88	1955	Adams	79	F	Yes	ASD	Yes	No	No	No	Died from obstructive jaundice
89	1955	Sodi-Pallares	18	M	No	PFO	Yes	Yes	No	No	Died after lung resection
90	1955	"	8	F	Yes	ASD†	Yes	Yes	Yes	Yes	—
91	1955	Halonen	25	M	No	No†	Yes	Yes	No	Yes	—
92	1956	Kilby	6	F	Yes	PFO	Yes	Yes	Yes	Yes	Died after closure PFO, autopsy
93	1956	"	8	M	Yes	ASD*	Yes	Yes	Yes	Yes	—
94	1956	"	7 mo	M	Yes	ASD*	Yes	Yes	Yes	Yes	—
95	1956	"	10	F	Yes	ASD*	Yes	Yes	Yes	Yes	—
96	1956	"	13	F	Yes	PFO‡ ASD‡	Yes	Yes	Yes	Yes	Died after closure PFO, ASD
97	1956	Mahaim	21	M	Yes	ASD*	Yes	Yes	Yes	Yes	—
98	1956	Brown	51	F	Yes	PFO	Yes	Yes	No	Yes	Expired
99	1956	"	15	M	No	?	Yes	Yes	Yes	Yes	—
100	1956	"	13	F	No	No	Yes	Yes	Yes	Yes	Expired
101	1956	"	9	F	Yes	?	Yes	Yes	Yes	Yes	—
102	1957	Blount	5½	?	Yes	No*	Yes	Yes	Yes	Yes	—
103	1957	"	8	M	Yes	ASD*	Yes	Yes	Yes	Yes	—
104	1957	"	21	M	Yes	ASD*?	Yes	Yes	Yes	Yes	—
105	1957	"	35	F	No	ASD*?	Yes	Yes	Yes	Yes	—
106	1957	Present case	14	M	Yes	ASD*?	Yes	Yes	Yes	Yes	—
107	1957	Present case	14	M	Yes	ASD*?	Yes	Yes	Yes	Yes	Sudden death
108	1957	Present case	24	F	No	No*	Yes	Yes	Yes	Yes	—

PFO = patent foramen ovale; ASD = auricular septal defect; VSD = ventricular septal defect.
* Evident at cardiac catheterization; † by angiocardiography; ‡ at surgery.

Review of the Literature

In reviewing the literature on Ebstein's anomaly, the collected data from 108 cases are herein reported (including the authors' three cases). Of this total, 55 have been diagnosed clinically and the remainder at autopsy. Of the 55 cases diagnosed clinically, seven have been confirmed at autopsy. Sufficient clinical and laboratory data (Table I) for analysis of Ebstein's anomaly were reported in only 79 of the cases reviewed (including the 22 summarized by Gøtzche and Falholt).[38] Of the 108 cases being reviewed 57 have been males, 46 females, and in 5 cases the sex of the patient was not mentioned. The age range was from 2½ days to 79 years. The average age at the time of death in 60 cases was 23 years.

Of the 57 autopsy cases, 46 have had defects of the septum (Table I). Forty-one of these had either a patent or fenestrated foramen ovale; five of these had in addition a separate auricular defect and one had a separate ventricular defect. Three other cases had auricular septal defects alone. One patient had in addition to a patent foramen ovale a defect between the right atrium and the pulmonary artery. Seven

cases had no septal openings and in three cases the presence or absence of a defect was not mentioned. Becu[55] reported a case of transposition with an Ebstein's defect but because the primary difficulty was not necessarily the tricuspid valve anomaly, we have not included the case in our review.

In 16 of the 108 cases reviewed there had been sudden death, five patients have had tuberculosis, three have had a brain abscess, and five had paradoxic embolization. Two patients have had severe systemic hypertension in addition to Ebstein's anomaly.

The severity of the reported symptoms and signs (Table II) caused by Ebstein's anomaly and the incapacity caused by this disorder have apparently been quite variable. Most patients have been markedly limited in their activities from an early age while a few have led almost normal lives till rather advanced ages.

TABLE II
Symptoms and Signs of 86 Cases of Ebstein's Anomaly

Dyspnea	68
Paroxysmal tachycardia	18
Fainting spells	6
History of rheumatic fever	4
Cyanosis	69
No murmurs	6
Systolic murmur	74
Rough	23
Soft	22
Loud	23
Moderate or faint	24
Localization at 3rd or 4th left ICS	35
Localization at lower precordium	24
Associated diastolic murmur	33
Gallop rhythm	
Triple	39
Quadruple	5

Dyspnea has been a complaint in 68 of the 86 cases analyzed. Paroxysmal tachycardia has been a problem in 18 cases. Six patients have had repeated episodes of fainting. Only rarely, if ever, are there complaints of orthopnea, paroxysmal nocturnal dyspnea, or ankle swelling.

Sixty-nine of the 108 patients studied had reported cyanosis at some time during their lives. It appears that most patients with cyanosis have it from birth or shortly thereafter, the average age of onset being approximately four years.

Patients with long standing cyanosis due to Ebstein's anomaly have sometimes been noted to have clubbing. In most cases the pulsations of the peripheral vessels have been noted to be weak; this is undoubtedly due to the low cardiac output. A few of the patients have been noted to have anginal-like chest pains.

Electrocardiograms revealed a right bundle branch block in 75 per cent of these cases (Table III). In two-thirds of the cases the electrocardiograms showed large P waves and one-quarter have had findings compatible with a first degree atrioventricular block. One-quarter have had abnormalities of rate or rhythm. The Wolff-Parkinson-White syndrome has been noted in six cases of Ebstein's anomaly.[38,41,46,65,67]

TABLE III
Electrocardiographic Findings in 86 Cases

Right bundle branch block	61
Enlarged P waves	52
Nodal rhythm	?
Ventricular premature contractions	17
Paroxysmal auricular tachycardia	18
Prolonged P-R interval	14
Probable right bundle branch block	5
T wave changes	4
Right axis deviation without RBBB	3
Wolff-Parkinson-White syndrome	6
Low voltage QRS	3
Left bundle branch block	1

Roentgenologic changes have been noted in 84 cases; of these, 78 were stated to have an increased cardio-thoracic ratio and 6 were normal. The left cardiac border was convex and elevated in 69 cases. Vascular markings were normal in 18 and reported as decreased in 32 instances. The pulmonary arch was reported prominent in only 4 cases out of 52. Not enough roentgenologic data was present for significant comment on definitive chamber enlargement in most cases.

Fifty-one of the 108 cases reviewed have had

TABLE IV
Cardiac Catheterization Data in 51 Cases

Case*	Atrium size estimated at catheterization	Catheterization of A.S.D.	Left to right shunt evidenced by R. A. saturations	Arterial O_2 saturation		Pressure mm Hg		
				Rest %	Exercise %	P.A.	R.V.	R.A.
Tourniaire	—	No	—	—	—	13/10	16/13	16/13
Engle 2	—	Yes	No	66	31	—	—	—
Baker								
1	Enormous	Yes	No	75	—	—	—	—
2	Enormous	Yes	No	93	—	—	—	—
Reynolds	Huge	Yes	No	79	—	—	—	—
Van Lingen								
1	—	No	Yes	87	76	22/10	22/4	7/4
2	—	No	Yes	69	55	22/10	22/8	9/5
Goodwin 2	Large	No	No	88	—	—	—	2
Broadbent								
1	—	No	No	75	—	18/10	11/3	11/4
2	—	No	Yes	89	—	20/10	19/4	10/4
3	Large	No	No	84	—	34/22	33/13	25/13
Gotzche								
1	Enormous	No	Yes	87	80	14/8	18/2	7/4
2	Large	Yes	No	89	84	16/4	27/2	8/2
3	Huge	No	No	93	92	17/10	22/0	15/3
4	Enormous	Yes	No	89	75	—	25/0	8/1
5	Huge	No	Yes	96	92	15/8	15/0	2
6	Large	No	No	90	75	16/6	24/2	3
Blacket 1	—	No	No	—	—	13/4	13/4	7/1
Henderson	Enormous	No	Yes	91	—	14	10	7
Kerwin	Very large	No	No	86	—	—	32/6	16/10
Medd	Large	No	—	—	—	—	18/4	8/4
Wright	Large	No	No	87	61	14/9	14/9	14/5
Bayer								
1	—	No	No	80	—	—	26/0	10/0
2	—	No	—	78	—	—	18/0	7/3
3	—	No	—	79	—	—	15/0	4/0
Schaede 1	—	Yes	—	—	—	—	—	—
Grob	—	Yes	—	97	—	30/15	30/0	15/0
Lenegre								
1	—	—	—	—	—	18	10	9
3	Very large	—	Yes?	—	—	12	8	5
4	Very large	Yes	Yes?	68	—	6.4	5.2	5.2
CPC[18]	—	Yes	Yes	68	—	17/4	14/3	7.5
Kistin	—	—	No	—	—	"Normal"	"Normal"	"Normal"
Brown								
1	Large	No	No	—	—	10	—	4
2	Large	No	No	—	—	—	—	14
3	Large	No	No	—	—	—	—	11
Blount								
1	Large	No	No	91	91	19/9	24/0	7/2
2	Large	No	No	76	—	20/9	24/4	12/5
3	Markedly enlarged	No	No	95	89	22/10	29/3	10/4
4	—	No	—	96	85	22/9	29/0	10/5

TABLE IV (*Continued*)
Cardiac Catheterization Data in 51 Cases

Case*	Atrium size estimated at catheterization	Catheterization of A.S.D.	Left to right shunt evidenced by R.A. saturations	Arterial O_2 saturation		Pressure mm Hg		
				Rest %	Exercise %	P.A.	R.V.	R.A.
Kilby								
5	Huge	No	—	82	74	18/5	15/2	7/3
6	—	No	—	92	—	19/4	22/5	9/4
7	—	No	—	85	—	—	25/6	7/3
8	—	No	—	93	—	30/13	20/9	12/9
9	Large	Yes	Yes	97	—	38/10	38/7	5/1
Maheim	Extremely large	No	Yes	94	94	17/7	18/5	10/5
Gasul 2	—	Yes	—	—	—	—	—	—
Cisneros	—	?	?	84	—	13.4	27.1	7.6
Sodi-Pallares								
4	—	—	—	—	—	17.9/?	18/?	5.0
Vacca								
1	Very large	No	No	93	82	26/14	26/0	13/6
2	Large	No	No	93	85	18/10	18/7	10/4
3	Tremendous	No	No	94	—	15/5	20/0	8/0

A.S.D. = Auricular septal defect. P.A. = Pulmonary artery. R.V. = Right ventricle. R.A. = Right auricle.
* The numbers after each author's name refer to his specific cases if there was more than one.

cardiac catheterization (Table IV). However, in eight of these the diagnosis of Ebstein's anomaly was not made until after death. Systemic arterial oxygen saturation was normal in only 12 out of 39 patients in whom this determination was reported and 6 of these became unsaturated with exercise. Pulmonary artery pressure was normal in 27 cases and slightly elevated in four patients. The right auricular pressure was elevated in 30 patients. The right auricle was reported enlarged by catheter probing in 29 patients. Twelve patients were reported as having had the auricular septal defect catheterized, but only two of these had a left to right shunt reported. Nine and possibly two other cases had a left to right shunt found in the right auricle.

Although the average age at the time of death in this series of patients has been 23 years, there have been survivals even to the age of 79 years.[51] If these patients escape brain abscess, paradoxic embolization, and tuberculosis, there is still the constant threat of sudden death. This is likely to occur with strenuous activity, surgery, or diagnostic procedures.

Five patients have had systemic-pulmonary artery anastomoses of the Blalock-Taussig or Potts-Smith type (Table I). All have died shortly after surgery. Three others have died after exploration for the possibility of creating artificial shunts, and three died following closure of a patent foramen ovale. One patient[40] has survived surgical closure of the auricular septal defect with definite improvement postoperatively.

Discussion

The basic pathologic defect in Ebstein's anomaly is the downward displacement of an abnormal tricuspid valve (Fig. 6). There is usually only one functioning valve leaflet, the others being rudimentary. Usually two cusps or portions of them are fused to form the single functioning leaflet. The characteristic feature is that this single, large, functioning valve leaflet is attached to the ventricular wall at variable distances downward from the annulus fibrosus, the usual site of origin of the tricuspid valve. Beyond its attachment to the ventricular wall the valve is still intimately positioned to the ventricular wall by short stubby papillary

muscles and is free only in its more distal parts. The overall appearance as viewed from the right auricular aspect is that of a large, single, concave, sail-like valve sweeping out into the right ventricular cavity from an abnormal downward position on the ventricular wall. This results in a transection of the right ventricle, the proximal portion becoming "auricularized" and the distal portion representing the small, narrow, functioning right ventricle. In addition, the malpositioned valve may be otherwise irregularly shaped, roughened, or fenestrated.

The right auricle is usually dilated and hypertrophied. In the majority of cases it has been noted that the wall of the "auricularized" portion of the right ventricle was extremely thin and atrophic. Most authors have considered this an integral part of the malformation with one exception reported by Edwards.[36]

The functional atrioventricular opening is formed by the free edge of the single valve leaflet and the ventricular septal wall and is smaller than usual. The site of normal attachment of the valve, the atrioventricular ring, is usually dilated. The single functioning valve leaflet has usually been considered capable of producing competence despite the fact that Ebstein's original case demonstrated obvious incompetence. There are relatively few cases which have indicated any severe degree of either tricuspid stenosis or regurgitation.

Hemodynamic Effects: The primary disturbance of cardiovascular physiology in Ebstein's anomaly is the decreased output of the right ventricle, resulting in low pulmonary blood flow. Because of the decreased volume of the functioning right ventricle, the receiving chamber composed of right auricle and the proximal portion of the right ventricle is unable to empty itself completely. Characteristic features are decreased pulse volumes peripherally and increased arteriovenous oxygen saturation gradients, which may lead to "peripheral" cyanosis during times of increased oxygen demands.

With increasing demands upon the cardiac output as the patient grows, the right ventricle is unable to increase its stroke volume and this results in the intolerance to exercise as shown by dsypnea and weakness. The right auricle and "auricular" right ventricle distend, and the increased pressure results in a right to left shunt when a septal defect is present or the foramen ovale becomes patent.

Roentgenologic Findings: Roentgenologic findings in Ebstein's anomaly obviously depend on the severity and duration of the malformation and upon whether gross cardiac dilatation has become superimposed. In early stages no abnormalities of contour or size may be seen;[20] however, in later stages the findings are more characteristic. The contour of the heart is almost globular with the left cardiac border convex and elevated; the upper portion of the right cardiac border is rounded and progressively becomes more prominent. The hilar vascular markings are usually decreased or normal and there is no prominence of the pulmonary artery. On oblique views it will be noted that the right ventricular wall approaches the sternum and

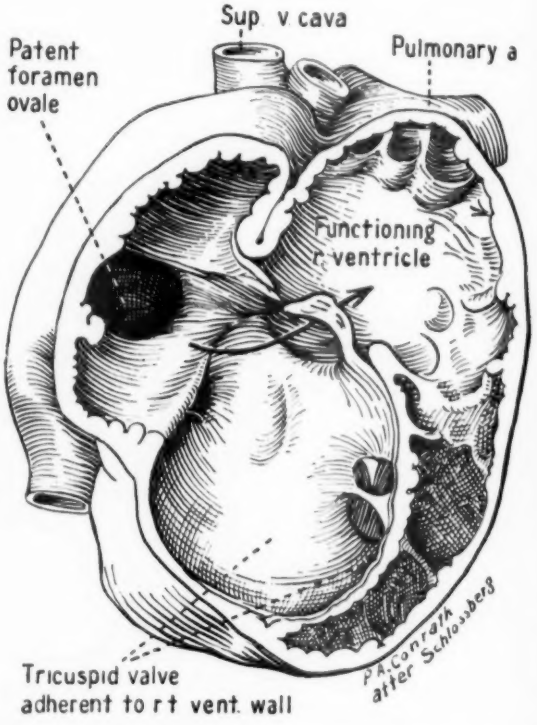

Fig. 6. Drawing of Ebstein's anomaly of the heart (after Schlossberg). This illustration demonstrates the large "auricularized" portion of the right ventricle encroaching upon the "functioning" portion of the ventricle. The large sail-like tricuspid valve is well seen here.

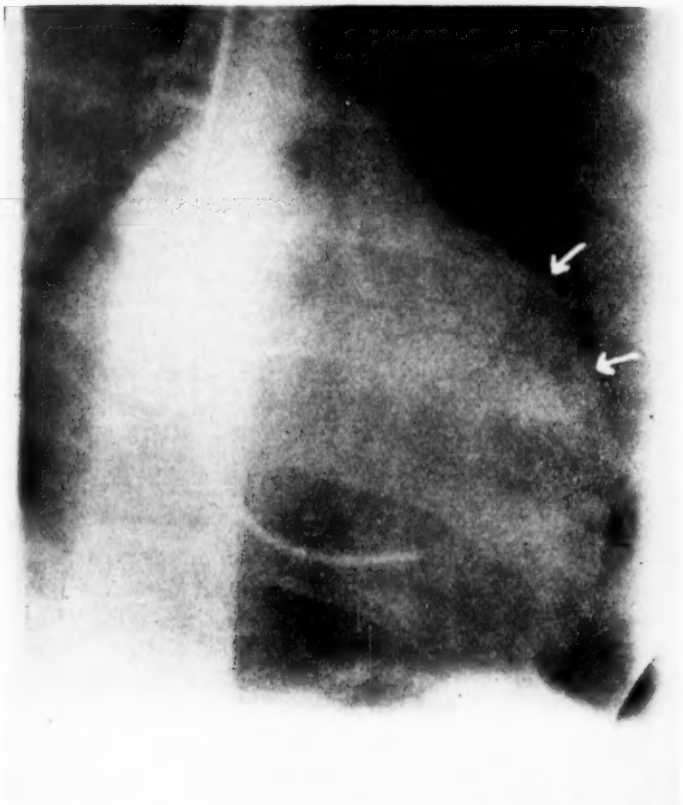

Fig. 7. Roentgenogram of the chest in a case of Ebstein's disease taken during cardiac catheterization. The catheter tip was recording an auricular pressure. Not until the catheter was within the limits of the arrows was a right ventricular pressure obtained. This condition existed in all three of our cases.

that the right auricle is enlarged. No left auricular enlargement will be noted on barium swallow.

Postmortem roentgenograms of the various chambers of the heart filled with barium were compared to the chest films of the patient reported by Bauer.[18] He was able to demonstrate that almost the entire cardiac shadow on a posteroanterior chest film was composed of the right auricle and ventricle with just the edge of the left ventricle forming the lower left border. The fullness in the upper portion of the right cardiac border represented the dilated right auricle. The elevated and convex left cardiac border represented the outflow portion of the right ventricle which had been displaced by the dilated "auricularized" portion of the right ventricle.

Angiocardiography: Angiocardiograms usually show a greatly dilated right heart and a marked delay in emptying of the right ventricle. The pulmonary vessels are usually poorly visualized. Blacket and his associates[31] state that in their cases both the right-sided enlargement and delayed emptying of Ebstein's anomaly were far greater than in any case of pulmonary stenosis they had encountered. A septal defect is often demonstrated by passage of contrast medium into the left auricle. The truly characteristic finding demonstrated in the films in four cases with angiocardiography was a curved, linear projection into the right heart representing the abnormal tricuspid valve arising from the ventricular wall.[26,31,50,68]

Electrocardiographic Findings: Our electrocardiographic data do not confirm that of Van Lingen and Bauersfeld.[54] The R′ height over the right precordium in our cases averaged

6 mm which is the maximum found in the cases which they analyzed. The concept that the height of the R′ in V_1-V_2 is an indication of the thickness of the right ventricular wall is open to challenge. Since the exploring electrode always records the net sum of the electrical phenomena going on beneath it, the height of the R′ depends greatly on the opposing forces arising or lacking in the relatively thick left ventricle. In complete right bundle branch block the right ventricular deplorization comes after that of the left ventricle and is thus unopposed. This lack of opposing force from the left ventricle may allow a large R′ without right ventricular hypertrophy.

Furthermore Meyers[57] has demonstrated that in most cases of right ventricular hypertrophy the maximum thickening of the ventricle is at the tricuspid ring and crista supraventricularis while the trabecular portions of the ventricle may hypertrophy little or not at all. Thus a maximum R′ may not be attained in leads from the V_1-V_2 positions which may be over trabecular portions of the ventricle, but only from leads further to the right such as V_3R-V_4R. This may or may not be the situation in Ebstein's anomaly but in the absence of these additional leads it is impossible to draw any final conclusions regarding the derivation of the low R′ waves which were reported in V_1-V_2 by Van Lingen and Bauersfeld.

The frequent finding of a right bundle branch block and enlarged P waves should make one suspicious of an Ebstein's anomaly whenever this combination occurs.

Catheterization Findings: In cardiac catheterization the catheter takes a very characteristic course during manipulation within the heart. As the tip of the catheter is maneuvered through the right auricle it will pass to the left border of the cardiac silhouette. At this point an auricular pressure is recorded rather than the usual right ventricular curve, due to the displaced valve leaflet and tremendous size of the right auricle (Fig. 7). When the tip of the catheter does pass through the tricuspid valve the ventricular outflow chamber appears to be extremely shortened. The catheter passes almost immediately into the pulmonary artery. Upon withdrawing the catheter across the pulmonary valve there is again evidence of what appears to be a small right ventricular chamber as measured by the absence of any recordable inflow chamber.

The right ventricular pressures are normal; however, the right auricular pressure is elevated in many cases. Left to right shunting of blood through the foramen ovale or auricular septal defect may be evident in the right auricular samples; however, a right to left shunt is more common.

Patients with Ebstein's anomaly apparently do not tolerate surgery or cardiac catheterization well. Two patients have died after cardiac catheterization. One of these had cardiac arrest just as the catheter reached the heart, was resuscitated successfully, but died suddenly several hours later; the other developed bilateral popliteal emboli after several days and died shortly thereafter. In an editorial note Maurice Campbell[71] states that one of his patients died as the result of cardiac catheterization and relates that Paul Wood had a patient with Ebstein's anomaly who died suddenly during cardiac catheterization; these two cases are not included in this series to our knowledge.

One patient died suddenly after angiocardiography. One had cardiac arrest and died during a sympathectomy for hypertension. Two died suddenly several hours after exploratory thoracic surgery, and one after lung resection.

Auscultation and phonocardiography play a prominent role in suggesting the diagnosis of Ebstein's disease, although the auscultatory signs are not sufficiently specific in themselves to be diagnostic of this condition. Until recently little emphasis was placed on these physical signs.

From Table II it is evident that a significant systolic murmur was present in almost every case. These systolic murmurs were usually loudest at the lower half of the left sternal border and were rough, soft, loud, moderate, faint or even rasping with the qualities of a friction rub.[13] In our three cases, the systolic murmurs were loudest at the middle to lower left sternal border, were grade 4 in intensity, and could be heard over the entire precordium.

The origin of this systolic murmur is in doubt. From catheterization studies, it is probable that before the onset of significant cardiac failure

these abnormal tricuspid valves are competent.[13,38] Occasionally the malformed valve may contain fenestrations. Turbulence within the large atrial reservoir must be great when the "auricularized" portion of the right ventricle contracts; it therefore seems feasible to us that a significant systolic murmur might be produced by this mechanism.

A diastolic murmur has been heard in slightly less than half the recorded cases (41 of 86 reviewed) but not in any of the three cases reported here. This would seem to have an obscure etiology.

The diminished first and the extra heart sounds in diastole are of considerable interest in this syndrome. Little attention has been drawn to the quality of the first sound and in most cases its intensity is not mentioned. In one of his cases Goodwin was impressed with its absence; in his other case no comment was made.[33] In all three of our cases the first sound was either greatly diminished or absent. The reasons for this we can only postulate. We ascribe to the thought that the first sound is mainly valvular in origin, and that only a small portion of the first sound is caused by closure of the tricuspid valve.[59] Therefore, we must conclude that in patients with Ebstein's anomaly this diminution of the first sound is due to lack of sound from the closure of the mitral valve and tensing of its chords. This may be explainable on the basis of low cardiac output. With diminished flow the mitral valve has probably ascended to a higher position at the time the left ventricle contracts, and hence a less intense sound is produced. In addition, some cases show a delay in the P-R interval which undoubtedly contributes to the diminution of the first heart sound.[60]

It has been stated that a gallop rhythm is commonly present in Ebstein's disease. We prefer to reserve this term for a single sound of low sound frequency, heard at the apical area or just inside the apex, occurring at the time of the early diastolic, rapid ventricular filling phase. This sound signifies a failing left ventricle and it cannot be distinguished from the normal third sound. We do not think the term should be applied here. We have been impressed by the dissimilarity between the early diastolic extra heart sounds in our three cases and those heard in the usual protodiastolic gallop. In addition, these extra sounds are identical in quality to the opening snap of the mitral valve in mitral stenosis. They are short, sharp, high pitched tones and are heard over wide areas. In regard to the etiology of this sound we are in agreement with Medd[39] that this early diastolic sound occurs at the time when the right ventricular pressure falls below that of the right auricle. In our first case the phonocardiogram, pressure records, and the electrocardiogram were compared. The early diastolic heart sound occurred when the right ventricular pressure fell during the period of isometric relaxation to meet the lower right auricular pressure. This would seem to indicate that this might well be the opening snap of the tricuspid valve.

Cases 1 and 3 each showed two extra diastolic heart sounds. Case 1 had a rate of 67 to 79 and case 3 a rate of 85 to 90 during the heart sound study. The early diastolic tones occurred 0.16 sec and 0.11 sec, respectively, after the second sound. The second extra heart sound occurred late in diastole at or shortly after the termination of the P waves. Case 2 had a heart rate of 109 to 115 per minute and a single extra sound was present in mid-diastole equidistant between the second and first heart sounds. In this case, as suggested by the wideness of the extra sound, this could represent a summation of sound. In both patients in whom the heart rate was relatively slow (cases 1 and 3) a fourth heart tone occurred after the P waves. These extra sounds met all the qualifications of auricular sounds. The second heart sound was not split in any of our cases and the quality was essentially normal. The P_2 was slightly diminished in each case and was less intense than A_2.

Differential Diagnosis: In the differential diagnosis the most likely condition to be confused with Ebstein's anomaly is pulmonic stenosis. Here the symptoms and possible evidence of cyanosis due to an associated auricular defect can be very similar. By auscultation the systolic murmur of pulmonic stenosis is at the base of the heart with a thrill usually palpable. In Ebstein's anomaly, the murmurs are lower on the left sternal border and extra sounds

are present. Roentgenograms of the chest may be similar in that the heart is enlarged and the lung vascularity is normal; however in Ebstein's anomaly there is usually a globular heart of rather large dimensions. The electrocardiogram in pulmonic stenosis will show right ventricular hypertrophy whereas the pattern in Ebstein's anomaly is often one of right bundle branch block and large P waves. The final diagnosis is determined by cardiac catheterization where a pressure gradient is demonstrated at the pulmonic valve in pulmonary stenosis but not in Ebstein's anomaly. In addition, an enlarged right "auricle" can be shown by the catheter positions within the heart.

Summary and Conclusions

Three cases of Ebstein's anomaly are reported; these plus 105 cases reported in the literature are reviewed and summarized. This disease produces a rather constant and highly characteristic group of findings which should be recognized.

The basic defect is a downward displacement of the tricuspid valve resulting in an oversized right auricle and small right ventricle. This in turn probably reduces the cardiac output. Cyanosis is present more often than not, being the result of a right to left shunt through an auricular septal defect or patent foramen ovale. Dyspnea and bouts of paroxysmal tachycardia are common complaints.

In our cases auscultation and phonocardiography revealed the combination of (1) a markedly diminished or absent first heart sound; (2) a moderately intense diamond-shaped, systolic murmur loudest at the lower left sternal border; (3) an early diastolic snapping extra heart sound heard over a wide area (opening snap of the tricuspid valve); (4) a late diastolic low pitched auricular sound.

The electrocardiogram usually exhibits a right bundle branch block and tall P waves.

Chest roentgenograms show an enlarged, globular heart with the left cardiac border convex and elevated. Normal or decreased pulmonary vascular markings are seen. Angiocardiograms demonstrate a greatly dilated right heart and marked delay in the emptying of the right ventricle; occasionally the displaced valve may be outlined.

Cardiac catheterization is extremely helpful and diagnostic. It usually reveals increased right auricular pressure. A septal defect may be demonstrated. Most characteristic is the observation of a huge right auricle and a small right ventricle as shown by the catheter positions.

One patient has survived cardiac surgery in which an associated patent foramen ovale was closed with definite clinical improvement.[40] Another patient survived cardiac exploration without definitive therapy.[68] As yet, no corrective action directed at the basic valvular abnormality has been reported. Survival to the early twenties is average. Demise is usually sudden, unpredictable, and unexplained.

Acknowledgment

We wish to acknowledge and thank Dr. James G. Janney, Jr., Director of the Department of Cardiology, St. Louis University, for the electrocardiographic interpretation and comments.

Addendum

A report by Kjellberg and associates in *Diagnosis of Congenital Heart Disease*, Year Book Publishers, Inc., 1955, page 518 gives the cardiac catheterization data on four cases not included in our report.

A recent article in *Circulation* 16: 1057, 1957 by Mayer and associates reports on ten new cases of Ebstein's anomaly. Three cases had cardiac catheterization data described with findings similar to those reported above. Four cases were confirmed by autopsy. One of these patients died during cardiac catheterization, and another after angiocardiography.

It is apparent that the clinical diagnosis of Ebstein's anomaly should not be taken lightly in view of the high mortality rate encountered in cardiac catheterization or angiocardiographic procedures.

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Conference on Hypertension

Modern Concepts of Hypertension and its Treatment

Moderator: JOSEPH H. HAFKENSCHIEL, JR., M.D., Director, Cardiopulmonary Unit, Lankenau Hospital
Panelists: EDWARD WEISS, M.D., Professor of Clinical Medicine, Temple University
WILLIAM LIKOFF, M.D., Associate Professor of Medicine, Hahnemann Medical College and Hospital
JOHN K. CLARK, M.D., Associate Professor of Medicine, University of Pennsylvania
CHARLES C. WOLFERTH, M.D., Emeritus Professor of Medicine, University of Pennsylvania

MODERATOR HAFKENSCHIEL: I am talking from my desk in Convention Hall, which is connected by a special circuit with the members of the panel in the color television studio at Lankenau Hospital.

Dr. Edward Weiss will lead off this conference with a short introductory statement on the general principles in the evaluation of patients with high blood pressure.

EVALUATION OF PATIENTS WITH HIGH BLOOD PRESSURE

DR. WEISS: A patient with hypertension often presents himself with symptoms of headache, dizziness, fatigue, and perhaps pain in the region of the heart, palpitation and shortness of breath. Or he may come just with the complaint of high blood pressure which has been discovered elsewhere. We have to determine if the patient has essential hypertension, and if it is essential hypertension should it be treated, and if so, how.

I will say at the very outset, although I know many will disagree, that I do not think that all patients with elevated blood pressure should be treated with hypotensive drugs. Nevertheless, every patient with an elevated blood pressure deserves as complete an initial study as can be done. This is important not only from the standpoint of diagnosis but also of prognosis. It establishes a base line for determining the future progress of the disease.

If the diagnosis of essential hypertension is at all questionable, certain tests must be made to rule out unusual causes of hypertension that can be cured by specific treatment. Certainly, hypertension is not a single disease, as can be seen in Figure 1. In this illustration, we see a a number of types of high blood pressure that have specific causes, tests and treatments. Even after a thorough initial workup, a repetition of tests may have to be done during the course of hypertensive disease if things do not go well. This is important when we supervise the care of patients over a long period of time.

Essential hypertension is a familial disease. A family history of death from heart failure or cerebrovascular accidents is strongly suggestive that we are dealing with essential hypertension. I should like to emphasize the importance of the eye ground examination, which often gives more information than the review of symptoms or the blood pressure reading. So far as the remainder of the study is concerned, I shall defer to other members of the panel, who will discuss in detail the role of the heart and kidney.

High blood pressure frequently makes its appearance in a setting of emotional stress, or, to be more exact, symptoms appear which are attributed to the hypertension. Whether the

* This conference was part of the Color Television Program of the Eleventh Clinical Meeting of the American Medical Association at Philadelphia on December 3, 1957. The discussion is made available through the cooperation of the Council on Scientific Assembly of the American Medical Association, the Smith, Kline and French Laboratories and the Department of Health Education, Lankenau Hospital, Philadelphia.

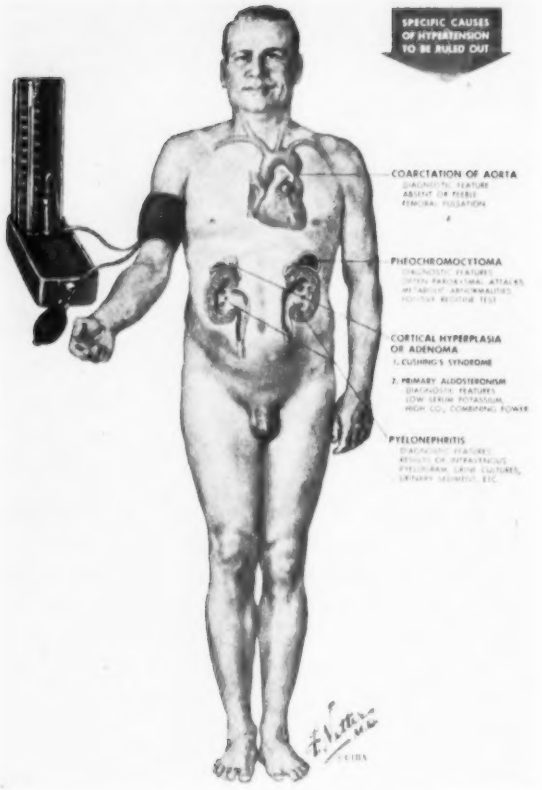

Fig. 1. Specific causes of hypertension to be ruled out in the initial workup of a patient with high blood pressure. Reprinted through the courtesy of Robert W. Wilkins, M.D. and Ciba Pharmaceutical Products, Inc. (Wilkins, R. W.: The Treatment of Hypertension. *Ciba Clin. Symposia* 9: 115, 1957).

hypertension is an evidence of personality decompensation is difficult to say. Often it is impossible to tell whether the high blood pressure did or did not precede the symptoms which led to its discovery. Nevertheless, as soon as the blood pressure elevation is discovered and the patient informed, a blood pressure phobia is apt to make its appearance. This phobia may become the dominant part of the clinical picture, and the symptoms then are only an exaggeration of the premorbid personality traits.

It is so easy for a physician to slap a blood pressure cuff on the arm of a patient and say, "It is your blood pressure." It is so difficult to spend time with a patient to try to gain an understanding about his emotional life. Once the diagnosis of high blood pressure has been established, attention is often centered on bringing the blood pressure down. The patient demands to know the blood pressure figures on each visit to the physician. He waits with anxious concern for the result of the latest reading. Frequently he has ideas of stroke or heart failure in the back of his mind.

In some instances of mild hypertension the best treatment is simply an effort to deal with this high blood pressure phobia by reassurance, minimal preoccupation with blood pressure figures, avoidance of weird diets and potent drugs, the advice to carry on in spite of symptoms, and above all, an effort to understand the patient as a person.

Thus, one almost must question the relation of the symptoms to the high blood pressure itself and make an effort to understand them from the standpoint of behavior. Our failure to deal adequately with hypertension stems in large part from our concern about bringing the blood pressure down, and from our failure to recognize the emotional origin of many of the symptoms that are attributed to high blood pressure.

Dr. Hafkenschiel: Dr. William Likoff will now discuss the effects of hypertension on the heart and cardiovascular dynamics.

The Heart in Hypertension

Dr. Likoff: Actually, the heart is not involved in the pathogenesis of hypertension. Nevertheless, it is quite clear that many patients with hypertension do have heart disease. Conversely, many patients with heart diseases are known to be hypertensive. It would appear, therefore, at least superficially, that there is more than a casual relationship between a sustained elevation in blood pressure and the development of a cardiac lesion.

At this early moment in our orientation to the over-all problem of hypertension, perhaps it is proper to define this relationship. Essentially, hypertension and the anatomic, pathologic, and functional cardiac disorders which develop subsequently are attributable to a single pathophysiologic event which precedes the elevation in blood pressure, namely, an increase in the peripheral vascular resistance.

For the remainder of the discussion I think it would be wise to repair to a diagram that has

been prepared for us by Mr. Richard Albany, of this city, which illustrates several phases in the development of the cardiovascular dynamics in hypertension. *Phase I* (Fig. 2) is that of normal cardiovascular dynamics. The heart is

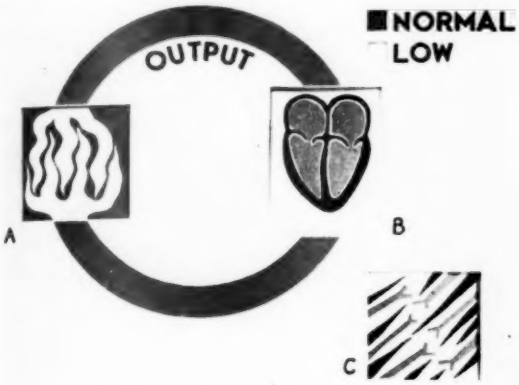

Fig. 2. Cardiovascular dynamics in hypertension (phase I). (a) Peripheral vascular resistance; (b) cardiac size; (c) ratio of capillary to myocardial cells. Under normal peripheral vascular resistance the cardiac output remains normal, as does the size of the heart, the thickness of the walls, and the ratio between the capillary and myocardial cells.

known to be able to maintain an adequate output against a reasonable peripheral vascular resistance. The system is so exquisitely balanced that it is possible for cardiac functions to be carried out with a very economical expenditure of kinetic energy.

In *phase II* (Fig. 3), for reasons that are not quite well understood, peripheral vascular resistance increases and a series of very important events transpire. In this second phase the heart maintains a normal output, but does so only through an increased expenditure of kinetic energy. This is a temporary compromise. With time, a *phase III* (Fig. 4) develops. The cardiac muscle hypertrophies, because the myocardium can then increase contractility with a more efficient expenditure of kinetic energy.

At this stage (*phase III*) the patient may be entirely well. However, the patient may develop objective evidences of his disease such as concentric hypertrophy of the left ventricle. This is demonstrated in Figure 5 which is a rather typical example of severe left ventricular hypertrophy. The patient's electrocardiogram under these circumstances is abnormal. Increased amplitude of the R wave, depressed RST segment, and inversion of the T wave may

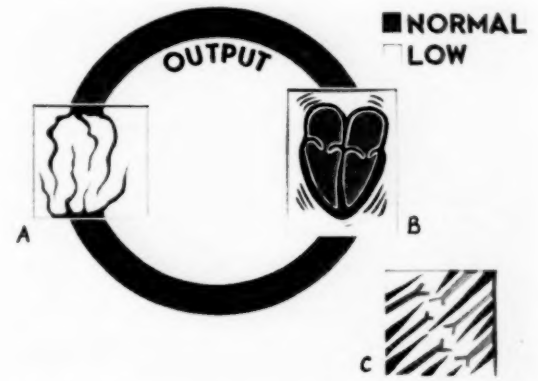

Fig. 3. Cardiovascular dynamics in hypertension (phase II). (a) Peripheral vascular resistance; (b) cardiac size; (c) ratio of capillary to myocardial cells. With increased peripheral vascular resistance the cardiac output remains normal, but only with expenditure of kinetic energy. The heart size remains normal as does the ratio of capillary to muscle cells.

be seen in bipolar lead I and in the lateral precordial leads.

The myocardial hypertrophy which has

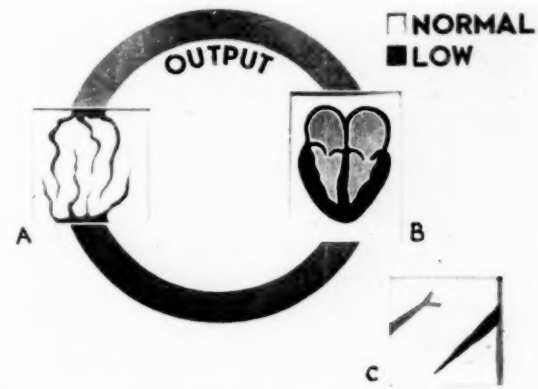

Fig. 4. Cardiovascular dynamics in hypertension (phase III). (a) Peripheral vascular resistance; (b) cardiac size; (c) ratio of capillary to myocardial cells. With continuing peripheral vascular resistance the muscle of the heart hypertrophies and a decreased ratio of capillary to muscle cell develops. The cardiac output may decrease.

been mentioned is only an initial response. Normally, a precise arrangement exists between the coronary capillaries and each individual

Fig. 5. Tremendous left ventricular hypertrophy in patient with hypertension.

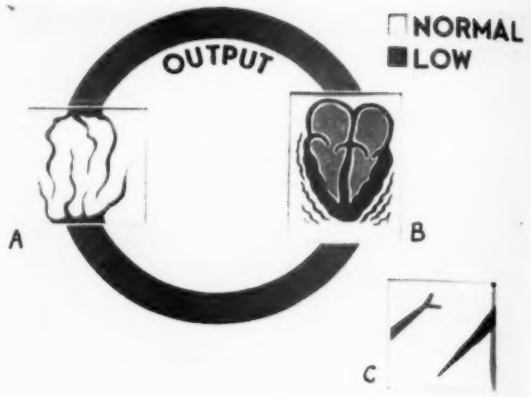

Fig. 6. Failure of cardiac mechanism in hypertension. (a) Peripheral vascular resistance; (b) cardiac size; (c) ratio of capillary to myocardial cells. With continued peripheral vascular resistance and a decreased ratio of capillary to myocardial cells, myocardial reserve is impaired, output falls and left ventricular failure ensues.

muscle fiber. With the development of hypertrophy the girth of each muscle fiber enlarges, and as a result the diffusion distance between these capillaries and the myocardial cell increases considerably.

A series of adverse metabolic events then develops (*phase IV*) which leads to the loss of muscle contractility, chamber dilatation, and inability of the heart to put out a normal output, and finally a failure of the entire cardiac mechanism (Fig. 6). Clinically, at this stage in the disease the patient may be quite ill. He may evidence his difficulty by easy fatigability, dyspnea on effort, paroxysmal nocturnal dyspnea, various cardiac arrythmias, or persistent peripheral edema.

This is not the only avenue by which the devolutionary pattern develops. Although hypertension does not cause atherosclerosis it is true that individuals with hypertension have a tendency to develop coronary artery disease more frequently. Hence, it is possible for a patient to develop acute coronary insufficiency with myocardial infarction, or diffuse myocardial fibrosis. In this manner the function of the heart may be additionally impaired.

In summary, it therefore appears that the heart in hypertension bears the brunt of a single pathophysiologic event, namely increased peripheral resistance. As a result a gradual revolutionary pattern develops, marked by increasing abnormalities in the circulatory dynamics which terminate in an advanced form of heart disease.

MODERATOR HAFKENSCHIEL: I will now present Dr. John K. Clark whose assigned topic is "The Role of the Kidney in High Blood Pressure."

ROLE OF THE KIDNEY IN HYPERTENSION

DR. CLARK: The kidney plays a dual role in hypertension, being sometimes the victim, sometimes the culprit, and sometimes both. As to the role of the kidney as the victim, it is quite generally agreed that all forms of hypertension have some impact on the kidney at either the functional or structural level. Obviously, the renal vascular bed shares in the general increase of peripheral vascular resistance mentioned by Dr. Likoff. There is some evidence that the renal vascular resistance may be increased out of proportion to that of the rest of the body, even at a time when total renal blood flow is within normal limits.

It is true that measurements of the renal blood fraction, namely, that fraction of the total cardiac output going to the kidney, have not demonstrated this to be the unequivocal case, but if one looks at the intrarenal hemodynamics, namely, the relationship between glomerular filtration rate and renal plasma flow, one inevitably finds an elevated filtration fraction. In other words, the kidney is filtering an increased volume of fluid from each unit of perfusing blood, indicating that a functional derangement at the hemodynamic level has occurred, even in very early hypertension.

Later in the course of the disease renal plasma flow is decreased below the normal range. This decrease in renal plasma flow subsequently results in a decrease in the mass of functioning renal tissue, as evidenced by more precise tests of renal function. At the clinical level, early in the course of hypertension, such symptoms as nocturia and polyuria may be present, and these are reflected in decreases in maximal concentrating power before a fixed specific gravity is reached.

As to specific enzymatic functions of the kidney, very little is known, although we strongly suspect that a more subtle impact of the disease has occurred at the enzymatic level. So far as functions which are easily measured, such as paraaminohippurate extraction, no abnormality is shown, the decreases in other tests simply being the result of structural abnormalities as atrophy of the kidney occurs due to progressive vascular disease. The vascular disease seen in the kidney is accelerated by the hypertension, and some of the vascular lesions may indeed be specific to the elevation of blood pressure.

As to the role of the kidney as the culprit in causing hypertension, it is perfectly clear that in some cases the kidney is obviously the cause of the hypertension. Whether the renal disease be unilateral, chiefly vascular, with or without associated obstruction, or bilateral, in the course of glomerular nephritis, pyelonephritis, congenital lesions or almost any of the forms of bilateral renal disease, the hypertension in these instances is obviously of renal origin. It would not be profitable to examine the precise nature of the renal disease resulting in hypertension, nor is it a matter of any particular profit to examine the extent of the renal disease, because the degree and severity of the hypertension seem to be quite independent of the renal functional impairment as measured by means available to us at the present time.

One possible avenue of investigation which has not been explored thoroughly is the possibility that whether or not a patient with renal disease develops hypertension may in part be related to the particular patient rather than to the particular form of renal disease, or in other words, an interaction between other predisposing factors and the renal disease.

Regardless of the fact that some renal disease is obviously associated in an etiologic manner with hypertension, what can we say of the possibility that all hypertension of the so-called essential variety is really of renal origin? We do not have the answer at present, although historically it is unquestionably true that the largest single block of essential hypertensives to be taken out of the essential category occurred with the demonstration by Weiss, Longcope and others, that pyelonephritis is a common disease and very frequently associated with hypertension. This applies also to unrecognized forms of renal disease of the less well-known variety which may masquerade as essential hypertension; for example, interstitial pyelonephritis with negative urine findings, a situation which fortunately is rare.

Another possibility is that the kidney may be involved in production of a pressor substance such as renin, as seen in some experimental forms of hypertension, or one of the many other substances that have been described. Or the kidney may be involved in a negative rather than a positive way. In other words, hypertension may be a deficiency of the kidney or failure to destroy a pressor mechanism which may be extrarenal in origin.

In addition, the kidney could be involved in the etiology of hypertension by some exaggeration of its physiologic response, namely, changes in excretion of aldosterone, changes in its responsiveness to sodium loads, or in a variety of poorly understood functions that we are incapable of studying at the present time. Lastly, there remains the possibility that the kidney may be involved etiologically in essential hypertension

by some totally unknown mechanism, and this is, of course, for the future to answer.

MODERATOR HAFKENSCHIEL: Let us turn next to Dr. Charles C. Wolferth who will speak on objectives in treatment.

OBJECTIVES IN TREATMENT OF HIGH BLOOD PRESSURE

DR. WOLFERTH: The basic objectives in treatment of patients with hypertension are, of course, the same basic objectives that we have in the treatment of all other types of disease. The modes of procedure naturally have to vary depending on the nature of the problems that have to be faced and the knowledge and resources we can bring to bear towards those problems.

First we have the problem of keeping well people well. Naturally, one thinks of prophylaxis. How far along are we in the prophylaxis of hypertension? If you were a visitor from Mars and had listened to my fellow performers on this program thus far, you would know already that we could not have gone very far in the prophylaxis of hypertension. We have been told already that it is a familial disease. There is certainly a hereditary factor in hypertension. This has been recognized ever since we first learned how to take blood pressure.

Are we going to educate young people to pick their conjugal partners with care, finding out whether their parents or grandparents had hypertension, to protect their hypothetical—hypothetical at that time—children 50 years from now? I think not. At least, I am a little pessimistic about it. If we can't do that what else can we do? We can try to persuade our obese patients to correct their faulty habits of eating. We can try to bear in mind some of the things that Dr. Weiss has told us about the psychogenic aspects of this problem, which are tremendously important, and we may be able to make them alter their mode of life if we are persuasive enough. We probably will not be persuasive enough because almost everyone has the feeling, "Well, it can't happen to me." We see this attitude in coronary disease as well as hypertension. Yet this is one of the great public health problems of the day. I would class it next to coronary disease as the number 2 public health problem. Many people die of other things, such as coronary disease and strokes, in which the actual important etiologic factor is hypertension.

Now, if I am a little pessimistic about the prophylaxis of hypertension, I am not so pessimistic about what we can do in the early stages of hypertension. Most people get their blood pressure taken nowadays. Some of them even get it taken on the boardwalk at Atlantic City and they come to you because their elevated blood pressure has been discovered. We need a case finding effort, just as diabetologists have used case finding efforts in their field.

We ought to know when people get hypertension because this is the time when we can do the most good. This is the time to make a complete careful physical survey including renal studies, with special reference to blood supply, pyelonephritis, and, in fact, any type of unilateral renal disease; to learn something about their physiologic make up; to treat their obesity, because now you have a compelling reason for cooperation. Bring to bear, by all means, all the psychologic skills you can in having these people learn and observe good mental and physical hygiene.

If these measures do not work, then I believe there is a place for drugs; not in every patient, of course, because some people just have high blood pressure when they come to the doctor. They must be actually hypertensive. As Dr. Weiss emphasized, you can determine that by watching their eyegrounds because practically all people who are really hypertensive begin to get changes in their eyegrounds which advance as the process endures. If the blood pressure cannot be controlled without drugs, we now have blood pressure reducing agents that have proven their worth and can be used to mitigate this disease.

We know now that there is a relationship between vascular deterioration, vital organ damage and high blood pressure. How close this correlation may be is not clear. The later stages of hypertension are highly useful to study various drug effects. If we cannot affect the blood pressure favorably in patients with severe grades of hypertension, then I am dubious about the value of these drugs in less severe cases.

The same applies to operations for hypertension. If you can improve the patients with Smithwick group 4 hypertension, who have not gone beyond the point of no return, then you have an operation that is of value. If you cannot improve such patients, then the operative procedure is open to question.

Finally, if we let our patients get to the point of no return without fighting every inch of the way to preserve their health, we have nothing to be proud of.

Follow-up Studies in Hypertensive Patients

Moderator Hafkenschiel: As your moderator I would like to present now my own personal experiences with 132 patients with high blood pressure who have been followed for five years or more. In this group of patients, who were studied before 1951 and were given a prognosis rating using the criteria of Smithwick at the time of the initial baseline examination, there were 77 men and 55 women. Follow-up studies of this group (Fig. 7 and 8) showed that 66 per cent are surviving after five years, with no significant difference in survival between the men and the women.

When the survival experience is plotted according to the original Smithwick grading, year by year, up to a five-year follow-up level (Fig. 9), we see that 96 per cent of all the group

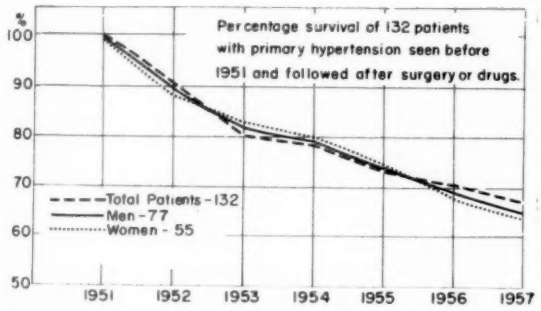

Fig. 7. Survival rates of 132 hypertensive patients followed for five years or more.

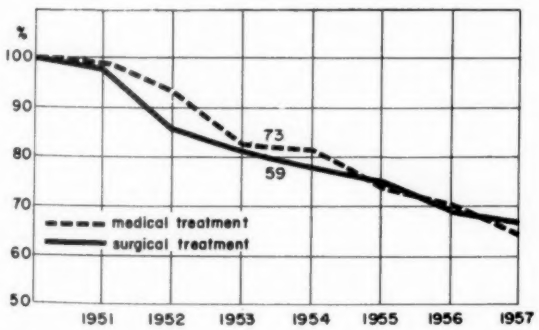

Fig. 8. Comparison of survival rates in patients treated with drugs and those treated surgically.

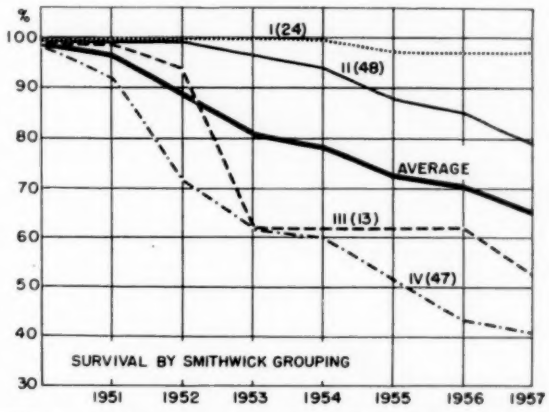

Fig. 9. Correlation of survival rates with Smithwick grading of hypertension at time of initial examination.

1 patients are surviving as compared to only 79 per cent of the group 2, only 53 per cent of the group 3, and only 41 per cent of the group 4. Thus, our small series indicates that the Smithwick criteria, when applied to a group this size or larger, seem to have some validity.

Because the curves of groups 1 and 2 and those of groups 3 and 4 are essentially the same, it might be helpful in this small series to compare the result of medical and surgical treatment in the patients in the good prognosis group, that is, group 1 and 2 combined, and in the patients in the poor prognosis group, that is groups 3 and 4 combined. In the good prognosis group (Smithwick 1 and 2, Fig. 10)

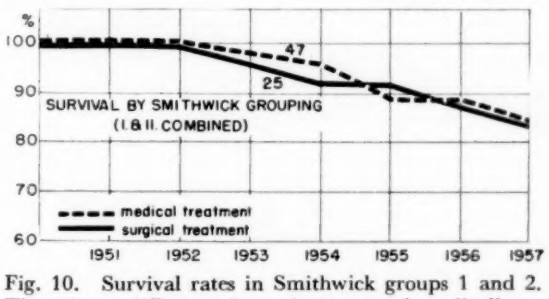

Fig. 10. Survival rates in Smithwick groups 1 and 2. There is no difference in patients treated medically or surgically.

85 per cent are surviving at five years, no matter what the treatment, whether medical or surgical. In the poor prognosis group, however, (Smithwick 3 and 4, Fig. 11) one sees that the

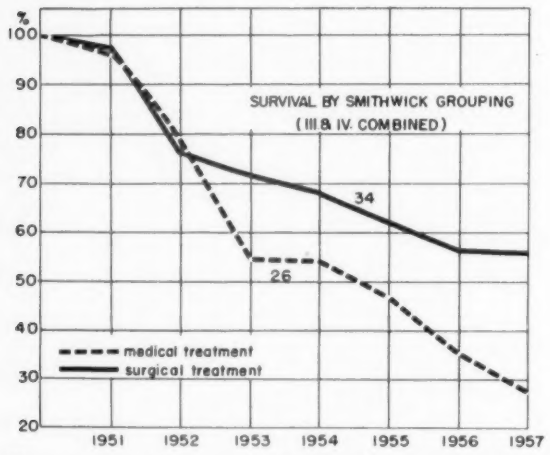

Fig. 11. Survival rates in Smithwick groups 3 and 4. Five year survival rate of medically treated patients is only half that of operated patients.

surgical approach is more favorable, with 56 per cent survival in the operated patients and only 28 per cent survival in those medically treated.

Now, what do we conclude? Our experience indicates that it is imperative that physician and patient agree to embark on an intensive depressor drug program or accept a recommendation for surgical management before the renal function has deteriorated or other vascular complications have supervened to an extent sufficient to put patients into the Smithwick classification of groups 3 and 4.

The organs involved in the vascular complications in patients with primary hypertension are the heart, the brain and the retina, and the kidneys. Most patients with involvement of all these vascular beds are in the Smithwick group 4 category. We wish to emphasize that essential hypertension is a disease the diagnosis of which is made by a process of exclusion, and that the blood pressure disturbance is perpetuated by both humoral and neurogenic factors.

Questions on Etiology and Pathogenesis

Moderator Hafkenschiel: We have several questions on etiology and pathogenesis. Here is one on hypertension in pregnancy. What have you observed to be the subsequent course of women who had elevated blood pressure, mild or severe, late in pregnancy?

Dr. Wolferth, I know you have definite opinions on this. Would you start the discussion?

Dr. Wolferth: Many of our audience may be too young to remember back to the time when the late Dr. Herrick of New York wrote his classic paper on this subject. Dr. Herrick supported the thesis that in a good many instances in women, hypertension had its start during toxemia of pregnancy; that following pregnancy these women might have a normal blood pressure for a while and then later, when they were away from under the eagle eye of the obstetrician, might develop hypertension that in all its manifestations was similar to what we call essential hypertension today.

Our obstetrical friends are vigorously opposed to this concept. They don't believe that it happens very often; at least I know that is true in the hospital where I do most of my work. But I have seen quite a good many women in whom this course of events took place, and I still believe that there is merit in Dr. Herrick's position, namely, that toxemia of pregnancy with hypertension at that time may be the initiating factor of hypertensive disease later on.

Moderator Hafkenschiel: Dr. Weiss, do you have any comment?

Dr. Weiss: I am old enough also to remember the Herrick papers, and I was very much impressed by them, as Dr. Wolferth was. My impression is, however, that subsequent studies have not borne out that there was such a high incidence of persistent hypertension following toxemia of pregnancy. Furthermore, the question has been raised as to whether these people were already predisposed, and that the toxemia simply precipitated the hypertension.

I do not know any way of proving this, but it has been suggested that just as the patient with convulsive toxemia may perhaps have had a convulsive tendency as shown by electroencephalogram, so the chronic hypertensive patient, who has apparently begun her career with toxemia of pregnancy, may have been

predisposed to essential hypertension before she developed her toxemia.

MODERATOR HAFKENSCHIEL: Dr. Clark, what about the kidney in pregnant women who have a tendency to retain fluid and may have a little albumin? How is that tied in with their possible later development of severe diastolic hypertension?

DR. CLARK: Before I get into that problem I would like to comment on the previous question. It seems to me in evaluating the number of women who have had toxemia and who subsequently develop so-called essential hypertension, we would have to be very sure that urinary tract infection, namely, pyelonephritis, had been ruled out. Pregnancy, of course, not specifically toxemia but pregnancy, predisposes to urinary tract infections, and a great many women with chronic asymptomatic pyelonephritis acquired it during their pregnancy. So one would wonder whether this had really been excluded in patients who subsequently developed hypertension.

I do not believe that I can answer the question relating to the endocrine disorders and fluid and salt retention in pregnancy, with subsequent development of hypertension. It seems quite clear that there is a physiologic tendency to retain sodium, presumably due to a great many different factors during the pregnancy, chief of which are endocrine disorders, not disorders but rearrangements. This tendency may be exaggerated but I do not believe that there is any demonstrable relationship between the physiologic tendency to retain sodium during pregnancy and subsequent hypertension.

MODERATOR HAFKENSCHIEL: Dr. Likoff, would you comment on some of these points? What is your approach to such young pregnant patients with hypertension?

DR. LIKOFF: In listening to the three panelists discuss this subject matter, I am impressed by the uniformity of opinion. I also agree with the thinking expressed in relation to this topic.

We all recognize that pregnancy may reveal a default in body economy which is expressed by an elevation in blood pressure. Whether the cause is a urinary infection, an endocrine disturbance, or any other obscure factor, remains to be proven. It still remains true that generally these patients continue on and become hypertensive at the conclusion of their pregnancy. This may be because the basic error is a continuing process, or it may be, as Dr. Weiss indicated, that it matures in future years.

I believe that the tendency of a hypertensive pregnant woman to become and remain hypertensive in later years is an indisputable fact.

MODERATOR HAFKENSCHIEL: The next question is directed to Dr. Wolferth. What abnormal vascular responses seen in hypertension and possibly important in its pathogenesis are abolished by adrenalectomy?

DR. WOLFERTH: Dr. Hafkenschiel may remember one patient who was operated on about eight years ago when we were operating our first cases. The thing that was abolished mainly was the feeling of tension that she had had for a good many years. This was a woman whom I had known practically since the day she was born. She volunteered this statement a few days after operation: "For the first time in ten years I feel calm." Her blood pressure was not down very much at that time. In fact, her blood pressure was very slow in coming down.

Now, what reflex was involved? I don't know. People as a rule do not get marked lowering of blood pressure immediately after adrenalectomy. They continue to have what we, in a perhaps cowardly way, call increased vascular reactivity; in other words, their pressure stays up for awhile and it is only after two or three months that a significant lowering occurs, unless you permit them to develop adrenal insufficiency.

There are many reflexes, a few which we are aware of and many more that we don't know about. I have not the slightest idea what reflexes are affected by adrenalectomy. When we get a good result following adrenalectomy, the blood pressure comes down. It may come all the way down to normal and remain there. We can see the loss of vascular spasm in the eyegrounds on occasion. I am not one of those who think that peripheral resistance is the sole factor in the hemodynamics of hypertension, but I can tell sometimes when spasm is relieved.

MODERATOR HAFKENSCHIEL: Dr. Clark, I know you have made some observations of renal function in patients who have had their adrenals removed so that they were totally dependent on substitution therapy. What would be your reaction to that question? What vascular responses are removed by adrenalectomy?

DR. CLARK: I am not quite sure that I know. Originally, we had hoped that adrenalectomy would differ from other procedures, medical and surgical, in that not only would one decrease the renal vascular resistance and maintain renal plasma flow when the pressure came down, but that we would actually get increases in renal plasma flow. It was hoped that perhaps for the first time we would have a means of approach to the hypertensive uremic, on the basis that it would be possible to manage salt-losing nephritis easier than hypertensive uremia. This was not borne out in subsequent experience, and I guess the best we can say for adrenalectomy is that it too, like other procedures, lowers renal vascular resistance. I suspect that the reactivity of the kidney is diminished, as witness the sensitivity to other blood pressure lowering procedures, particularly drugs, following adrenalectomy.

DR. WEISS: Dr. Hafkenschiel, I know that this is not intended as a definitive discussion of adrenalectomy for hypertension, but just in case we do not get back to it later I should not like this audience to feel that every member of this panel is in favor of adrenalectomy for hypertension.

MODERATOR HAFKENSCHIEL: I am glad you brought that out, Dr. Weiss.

DR. WEISS: I know that is not the question that was raised. Just in passing I would like to say that losing one's adrenals is a very big price to pay to become calm, when there are many other ways of becoming calm. The removal of symptoms in a patient with hypertension is no proof that that therapeutic procedure is the proper one. We so often hear after various surgical efforts to deal with hypertension, "the blood pressure was not influenced but the patient felt better," as though that were ustification for surgery. I do not think it is. You can remove symptoms in patients with hypertension by various means, and we don't have to use extensive surgery or the removal of the adrenals for that purpose.

MODERATOR HAFKENSCHIEL: Dr. Likoff, I feel duty-bound to give you a chance to air your opinions about adrenalectomy for hypertension. May we have some comments from you?

DR. LIKOFF: The time has arrived for our first differences of opinion. I must take issue with Dr. Weiss on a small point, namely, that the cure of symptoms is not a measure of a therapeutic effort. I take issue on the basis of the fact that hypertension is a chronic disease, and in that disease, as well as other forms of cardiac disease, patients become well versed in the symptomatic pattern which they possess. I have a great deal of respect for the ability of such patients to assay their response to a therapeutic measure. I realize that Dr. Weiss is referring to the fact that many of the symptoms in hypertension may not arise from the disease itself.

In regard to adrenalectomy, I have had but a very modest experience with the procedure. I have advised it on very few occasions, and on those occasions have been disappointed. The failure, however, may be not in the procedure but in my inability to assay the indications for the procedure.

MODERATOR HAFKENSCHIEL: The etiologic basis of hypertension might be summarized as being of three possible factors, all interwoven: first, a history of hypertension in parents; second, a possible kidney basis; third, last but not least, the personality inside an individual.

Before we finish this subject I will ask Dr. Weiss to make a few comments on the presence of a particular type of personality in patients who have severe diastolic hypertension, such as 120 mm or higher even at bed rest.

DR. WEISS: I do not believe there is a specific personality that predisposes to hypertension. In other words, you cannot take a cross-section of the population and say this person is going to develop hypertension and this one is not. Everybody can get hypertension, from a normal, well-adjusted individual, to one who is psychotic.

In general, however, it can be said that increased tension does exist within people who have hypertension, and I often say this to

people who have high blood pressure and who complain of symptoms. This permits them to discuss their problems. It provides an easy stepping stone from physical to emotional factors. However, although emotional factors have, in general, a good deal to do with the symptoms that are attributed to hypertension, and may have something to do with precipitating hypertension in a predisposed individual or with aggravating hypertension in one who already has it, I cannot say that emotional factors cause hypertension, nor can I say that dealing with them effectively removes the hypertension.

Parenthetically, the test for a therapeutic procedure is not the removal of symptoms but, can we lengthen life or change the progress of the vascular disease that accompanies hypertension.

Questions on Evaluation of the Hypertensive Individual

Moderator Hafkenschiel: We will now consider some questions on the evaluation of the individual patient, and the first one is directed to Dr. Likoff. What does a difference of 20 mm or more in the blood pressure of the arms indicate?

Dr. Likoff: Many problems of great interest are involved in that question. We must start with the most fundamental one, namely, the mechanics of taking and recording the blood pressure.

The failure to put on a cuff snugly and carefully deflated may contribute to unusual and incorrect values. At least in my experience there is a reasonable difference in the blood pressure between the left and the right arm of many patients. The pressure may be elevated by as much as 10 mm of mercury in one arm on one occasion, and on a subsequent visit the reverse may be true.

I routinely record blood pressures in both the upper extremities, and automatically feel for the femoral pulses, because very obvious diagnoses may be confirmed or eliminated by that simple procedure. I believe that a 20 mm difference of pressure in both arms is unusual, and congenital anatomic difference in the vascular tree of one limb would be the most likely cause.

Dr. Weiss: May I ask whether the difference in blood pressure readings in the two arms is related to differences in the size of the hands or arms?

Dr. Likoff: That is a most interesting question, Dr. Weiss, and I do not think I can adequately answer it. I do know that where the biceps, for example, is of tremendous girth, very often the cuff is inadequate to record proper pressure because it fits poorly. Conversely, in a small child this also holds true. But I am not sure that the girth makes any difference at all if the pressures were properly recorded.

Moderator Hafkenschiel: Here is another question on evaluation, Dr. Clark. What is a classification of the renal diseases causing hypertension that one would think of in the baseline examination of a patient with high blood pressure?

Dr. Clark: It is easier to prepare a list of the renal diseases which are seldom associated with hypertension than those which are associated with hypertension. In the first group are the nephrotoxins which rarely result in hypertension unless the degree of renal insufficiency progresses to almost total anuria. Amyloid disease and tuberculosis of the kidney are rather rarely associated with hypertension. Other than these any of the remaining renal diseases may or may not be associated with hypertension.

It seems to me that one reasonable rule of thumb is something like this. If there is severe hypertension associated with very minimal urinary findings, the hypertension is unlikely to be due to glomerular nephritis or one of the parenchymatous renal disorders. If, on the other hand, there are marked urinary findings and the hypertension is mild, say 160 to 170 over 90 to 100, a renal origin is quite likely, but one will recognize that there are many exceptions both ways.

Moderator Hafkenschiel: Here is a question which raises a very basic point. Can the initial examination of a patient with a diastolic blood pressure above 110 be satisfactorily accomplished on an outpatient basis? Dr. Wolferth, what are your views on this basic question? Do you always require several days of

hospitalization to do a good initial examination?

DR. WOLFERTH: The first thing is to establish whether that patient's diastolic blood pressure actually runs around 110 or whether the patient is scared when he comes to see you and is afraid of what you are going to say. If the diastolic pressure actually runs around 110, then we can assume that we are dealing with a problem of some importance. As I stated in my opening remarks, this is the time that the patient ought to be studied thoroughly. You can make most of these studies in an office or clinic. You can certainly examine the urine, look at the eyegrounds, fluoroscope the heart and take an electrocardiogram. You can have an intravenous phenolsulfonephthalein test done in your office if you are careful and sure that you get good collections of urine.

There are some things that you cannot do in the office that you may want to have done, and these include most renal studies. I don't know whether Dr. Clark can tell us anything about blood flow in the renal arteries by his methods of studying renal hemodynamics. I do not like aortograms very much because of the complications that may occur. We have had some luck with retrograde aortograms made by inserting a catheter in the femoral artery, guiding it upward and then injecting the radio-opaque substance opposite the renal arteries. I am hopeful that the method that is now being considered, of studying the renal uptake of radioactive iodine, will help us along those lines.

If we need to have a patient catheterized for retrograde opaque studies of the renal pelves, such studies should be made in a hospital.

MODERATOR HAFKENSCHIEL: Dr. Clark, are you doing as an outpatient procedure bilateral retrograde kidney catheterization to study differential sodium concentrations and urine volumes to try to pick out which patients should have an aortogram made proximal to the renal arteries, and thus find out which kidney has an impaired blood flow?

DR. CLARK: We have not been doing them, although preliminary reports of such studies are extremely encouraging, showing that in trying to evaluate unilateral renal disease, changes in urinary volume and sodium concentration may reveal the presence of unilateral renal disease which is responsible for the hypertension.

Excluding this particular test, which remains to be evaluated in more cases, there are many subjects with unilateral renal disease whose intravenous urograms and differential tests are within the variation seen in ordinary hypertensive or normotensive subjects, and in these subjects I believe that we must do aortograms if we are to establish the unilateral or bilateral nature of the renal vascular lesion.

MODERATOR HAFKENSCHIEL: Dr. Likoff, I know in your hospital your x-ray department has been testing ways of visualizing blocked arteries in different parts of the circulation. Have you had any experience with these technics in relation to impairment of flow through the renal artery that might be at the basis of a severe diastolic hypertension?

DR. LIKOFF: As you implied, we do use the radio-opaque substances for vascular studies rather extensively, and although we share the same hesitancy about overdoing it, we have used it in an effort to determine whether or not unilateral or bilateral renal disease is present. Under these circumstances, when the test is precisely and carefully carried out we get very beautiful results indeed, and we have been gratified. I certainly would echo Dr. Wolferth's statement that it is not to be done glibly, but only on precise indication.

DR. WEISS: Dr. Hafkenschiel, may I comment? I think there is one other consideration in this question of outpatient versus hospital study, and that is that so often when we put patients in the hospital we observe within a few days that the blood pressure has dropped without treatment, simply as a result of the rest, and, I should add, the security that they feel in the hospital. Therefore, before we begin treatment with potent drugs or surgical measures, the question might be posed whether it isn't advisable to put the patient in the hospital to see whether a few days there, granted that we are studying rather than treating the patient, will nevertheless make a great difference in the level of his blood pressure and in our conception of the severity of the disease.

Questions on Treatment of Hypertension

Moderator Hafkenschiel: We have several questions on prophylactic treatment. I would like to refer to Dr. Wolferth this question that bears on the natural history of untreated hypertension. Can a patient with essential hypertension for many years become normotensive spontaneously? Can this occur after stopping drug therapy and under what situations?

Dr. Wolferth: The commonest cause of what we call "burned out" hypertension is coronary thrombosis. Years ago the most effective method for "treating" severe hypertensive disease was a large coronary thrombosis, which would often reduce the blood pressure to normal. Then the patient might do better symptomatically save for new cardiac symptoms. As a matter of fact, he might even in the long run do better cardiac-wise, although there is a tendency for blood pressure to go up again.

Blood pressure is a notoriously uncertain process. In mild hypertensives one of the reasons why so many treatments in the past have been regarded as of value, and I think, Dr. Weiss, these would include psychologic treatments on occasion, is that blood pressure may be elevated for awhile, then come down with or without benefit of treatment and then go back up again. But even if we limit our observations to cases of severe hypertension, every once in a while somebody will suffer from high blood pressure for years, then for reasons that we do not well understand develop normal blood pressure, and from then on the pressure may be normal for years. As I indicated I always look for possible myocardial infarction as the cause of this, but there are many times that we cannot find something of the sort.

So I must say that hypertension, except in its very late stages, is very apt to be a notoriously irregular condition, and that it is not so unusual for the pressure to come down to normal for awhile.

Moderator Hafkenschiel: What about your observations on patients who have been on rauwolfia for a period of time and had a lowering of their blood pressure? Have you observed their blood pressure to remain down indefinitely—six months, a year, two years—after the rauwolfia had been stopped?

Dr. Wolferth: I would be highly pleased if I observed that very frequently. It seems to me that after a period of time, usually a matter of several weeks or more, the blood pressure will begin to go up. But I suppose we do have to remember the unreliability of elevated blood pressure and recognize the fact that spontaneous remissions of hypertension may occur. I am not convinced that you can produce permanent reduction of pressure unless you have had patients on these drugs a long time. Then perhaps their vascular reactivity, if I may again use that term, may lessen.

Moderator Hafkenschiel: Dr. Likoff, do you have any comments on this subject?

Dr. Likoff: The time is short and it is dangerous to make categoric statements. I am almost willing to say that once a patient has been placed on a antihypertensive drug and does not represent a transient hyperreactor, the likelihood is the patient will not be able to sustain normal blood pressures without the aid of that drug or a substitute.

Moderator Hafkenschiel: Dr. Clark?

Dr. Clark: There have also been reports which suggest that once a patient's pressure is brought down, particularly with ganglionic blockade, not only is he unlikely to maintain a normal pressure if the drug is stopped but if the drug is stopped he is likely to have an accelerated phase of hypertension and go very promptly into left ventricular failure.

Moderator Hafkenschiel: That is a phenomenon that I have seen in our own clinic, where we have been a little too eager with the use of placebos to test what have been good results. We have observed vascular catastrophes when the potent depressor substances have been removed.

I now have a request for consultation of the management of a specific case. How would you approach the treatment of a brilliant hyperkinetic, aggressive executive of the pharmaceutical industry, aged 45, with a family history of hypertensive renal disease, in Smithwick group 2, but with advanced grade 2 hypertensive retinopathy and normal renal function? The

response of blood pressure on ordinary medical management including tranquilizers, veratrum, ganglionic blockade, has not been impressive. Dr. Weiss.

DR. WEISS: I do not know what being in the pharmaceutical industry has to do with this hyperkinetic individual.

MODERATOR HAFKENSCHIEL: He probably knows all the drugs.

DR. WEISS: That might very well add to the difficulties of treatment. The first thing to do is to find out a little more about the patient as a person, before deciding on any further measures such as surgery. I would want the patient in the hospital for a short period of observation and while he was there, while I was studying him in other ways, I would also be trying to get to know him as a person. In that way it is conceivable that we could understand him well enough and modify his environment or change his attitude sufficiently so that some of the measures that were used before and didn't seem to work would work now. I would certainly give the medical approach further trial before I recommended surgery for a patient such as this.

MODERATOR HAFKENSCHIEL: Dr. Likoff.

DR. LIKOFF: I noted that Dr. Weiss in his discussion about the effectiveness of psychotherapy in reducing blood pressure made the very pertinent remark initially that these patients do feel better, their tension is removed, but their hypertension remains. This, I believe, is a very critical point. In an individual such as this, one must recognize that after all the psychiatric groundwork has been done, we still will remain with an ill patient.

It seems to me that if we are to put any trust and faith in the more radical approaches to this problem, and there are occasions when we must, that it is by far better to do so early in the so-called terminal phase of the disease, rather than, as has already been expressed by the Moderator, later when the chances of reclamation are indeed slim.

I go along, therefore, with Dr. Weiss to the extent that I too would like to know his personality background, his difficulties, and the reasons why he is not responsive. However, I would like to go further and say I do not think this information would make much difference because a radical therapeutic approach will have to be employed.

MODERATOR HAFKENSCHIEL: Dr. Clark, I would like to have you comment on this problem. You may recall that this consultation request included the fact that the patient had normal renal function.

DR. CLARK: If he has normal renal function one can say that none of the more radical procedures are contraindicated. In other words, you can do a sympathectomy, or adrenalectomy, or both, without getting into trouble from a renal point of view. One would want to be sure that we were not dealing with one of the reversible forms of hypertension, and presumably this has been ruled out. In this particular age group with long duration of the disease, the chances of its resulting from unilateral renal vascular disorders seem to be remote, particularly in view of the strong positive family history, although I suppose this must always be considered, particularly if there has been a recent acceleration of the disease.

Let me ask you, Dr. Hafkenschiel, have the reversible forms of hypertension been adequately excluded here?

MODERATOR HAFKENSCHIEL: I can't be certain from the information that I have in front of me. It would appear to be primary hypertension.

Dr. Wolferth, would you comment on what you would think might be a diagnostic and therapeutic approach to such a patient problem?

DR. WOLFERTH: I do not suppose Dr. Weiss and I are so far different as one might think from hearing him inveigh against the use of adrenalectomy to produce calm in patients. After all, we don't do adrenalectomy just for that purpose.

I would dislike very much to do a formidable operative procedure such as adrenalectomy plus sympathectomy in a patient like this. But with a fatal outcome staring me in the face, if my friends do not approve of adrenalectomy, I would ask whether they prefer to have a dead patient. In our patient here, unless he developed some catastrophic vascular accident, such as a very severe cerebrovascular accident or coronary obstruction, the latter of which as

I indicated before might be a blessing in disguise, we would want to be perfectly sure that there was no alternative approach to the problem. For example, Dr. Clark might be able to tell us how near we are to discovering a neutralizing agent for what some people regard as the incretory product elaborated by the kidneys, which combats hypertension. In a recent paper the author propounded this thesis as though this discovery might be just around the corner.

I would like to see this person treated by the most penetrating psychologic methods. In view of the kind of person you said he was he probably could outtalk the psychiatrists on Freudianism, but whether that brand of therapy would help him or not is beyond me. But I emphasize again that I would resort to surgery only when I believed that there was no alternative.

MODERATOR HAFKENSCHIEL: Let us now turn to another question on treatment. Are there any bad effects from the therapeutic lowering of moderately severe hypertension to normotensive levels? Dr. Clark, you have had a chance to see patients with borderline renal function who have had sympathectomy, or adrenalectomy, or ganglionic blockade. What are some of the bad effects that you have observed?

DR. CLARK: This, of course, is always a source of worry or apprehension, that by lowering the blood pressure one may actually cause impairment of blood flow to one of the important vascular beds, the kidney, the myocardium, or the brain; we have all seen instances where this has occurred. For the most part, however, speaking now from the standpoint of the kidney, except in the face of extreme renal insufficiency, when the blood pressure is lowered the renal vascular resistance seems to go down in a parallel fashion; so that renal function is not further impaired and in fact may be improved. This applies to albuminuria, hematuria and renal vascular constriction secondary to minor degrees of congestive failure.

I think the crux of the matter is the speed with which the circulatory changes are brought about. If the circulation is changed abruptly and rapidly, there may be a temporary decrease in renal blood flow and glomerular filtration rate, but with long continued chronic therapy, renal function is usually very well maintained.

MODERATOR HAFKENSCHIEL: Here is a question I would like to direct to Dr. Likoff. What would you say about a low cholesterol diet in the prevention of hypertension?

DR. LIKOFF: One must realize that in speaking about cholesterol and its relationship to the pathogenesis of atherosclerosis we are speaking about a concept. It is extremely difficult, having only theoretic knowledge, to apply it seriously as a prophylactic measure. It is most difficult to apply this concept in actual therapy when a patient has all the manifestations of coronary atherosclerosis in the form of angina or a myocardial infarction.

We must take heed too, of the very many things that Dr. Weiss has said about the psyche and the trauma that results from the maladjustment of a personality to disease, particularly a hyper-reacting disease such as hypertension. It is difficult enough to subject such patients to the ordinary adjustment of habits in relationship to their work and attitude about life without superimposing upon them the difficulties encountered within a low cholesterol diet particularly when there are doubts about its value.

I speak like this even though I do not apply such dietary restrictions to the therapy of those who have overt evidence of atherosclerotic heart disease.

MODERATOR HAFKENSCHIEL: Here is a question I would like to direct to Dr. Weiss because some of the opening statements he made appear to be somewhat controversial.

Would you embark on a specific therapeutic program, such as rauwolfia plus veratrum or hydralazine, or dibenzyline, in combination, in a young individual in Smithwick class 1 who is otherwise asymptomatic? By that I would deduce that the questioner has in mind somebody with a diastolic pressure that is always 120 or more, as an outpatient.

DR. WEISS: When you say a therapeutic program, I take it to mean more than the use of drugs. I think that there is a therapeutic program for a patient who has hypertension

because hypertension is a sign that something is wrong and it is up to us to discover what is wrong if we can, and treat that. Just bringing the blood pressure down is not my idea of an adequate therapeutic program for a patient of this kind. I think that we ought to study this patient as carefully as we can from a total standpoint, which means a cardiovascular survey as well as a psychosomatic study, and then decide whether we want to use tranquilizers, for example, or one of the old-time sedatives, in addition to such other measures as may be indicated for obesity or other complication, or for some personality problem that has arisen.

I have seen a good many patients helped by rauwolfia, not necessarily because it brings the blood pressure down but because it produces this calming influence that we talked about. I have had many patients say that they felt calmer after taking rauwolfia. They demonstrated to me that the vasomotor flush which had crept up on the chest and neck had diminished under the influence of rauwolfia. As tensions are reduced one gets an opportunity to know the person and his problems and work more effectively from that standpoint.

It is not the blood pressure reduction in itself that I am so concerned about. I don't think that we ought to concentrate our attention so much on bringing blood pressure down, as on the total problem that is presented by the hypertensive patient.

MODERATOR HAFKENSCHIEL: Dr. Weiss, I would like to interrupt with a question that might bear on this. If it isn't the blood pressure that gets people in trouble what is it that makes them go from a Smithwick 1 and 2 classification now to a 3 or 4, five years from now?

DR. WEISS: It is, of course, the blood pressure elevation and the associated vascular disease. But it is also important to know what other elements may be contributing to the rapid progress of the hypertensive disease, emotional problems for example. Nevertheless, I am willing to agree that in the accelerated form of hypertension, so-called malignant hypertension, it has been demonstrated that ganglionic blockers prolong the life of these patients. Beyond that I have not seen any adequate demonstration that the drug treatment of hypertension prolongs life or changes the course of the vascular disease. Until that evidence is forthcoming I think we have to be careful about administering potent drugs and making people so blood pressure conscious.

MODERATOR HAFKENSCHIEL: Dr. Clark, what contribution do you think the deterioration of renal function makes in the progression of people that are in Smithwick groups 1 and 2 today but who have a severe diastolic hypertension and progress toward a Smithwick group 3 or 4 five years from now?

DR. CLARK: It seems to me that most individuals can tolerate moderate degrees of blood pressure reasonably well without getting into trouble. In the natural course of the disease, when their kidneys deteriorate badly, particularly to the point where they become azotemic, they then deteriorate very rapidly and have a very short time to live, in my experience. I am not sure which comes first, whether the renal deterioration is merely a part of the overall situation or whether it in itself contributes to the more rapid systemic deterioration. The chief purpose for following renal function very carefully in the type of patient that you describe is to be able to do something of a more radical nature before the kidney function has deteriorated to the point where such procedures are contraindicated.

MODERATOR HAFKENSCHIEL: Dr. Wolferth, in patients with hypertension without symptoms, in an age group of the early forties, what "prophylaxis" would you use? The question seems to stem from your opening remarks.

DR. WOLFERTH: I expected to be punished for those remarks. We have heard statements from this panel that were more or less directed toward this stage of hypertension. The education of patients ensures that you can't hide from them the fact that they are hypertensive, but you can at least try to produce an attitude of mind in them that perhaps hypertension is not the calamity that they may have thought it was originally. It is highly useful to get over this fear. Perhaps this is one of the reasons why some get calmer. What should you do when questioned about the blood pressure

level? You don't have any right to lie if they ask you what it is, but you can at least place it in its proper perspective.

I am strongly for placing first on the agenda types of treatment that do not utilize drugs. I think drugs including tranquilizing drugs should come toward the end of our program. The measures of education, psychic readjustment, and good habits of life should come first and their effects evaluated. If we watch these patients carefully and do not observe deterioration, the chances are we are not in serious trouble just then. But finally, when we come to the point when we cannot control levels of blood pressure that are too high, I would certainly say a persistent diastolic pressure of 120 is too high because patients who run pressures like that are going to deteriorate sooner or later, then I have no hesitation in using antihypertensive drugs. As stated previously, I don't know exactly what the correlation is between blood pressure levels and deterioration. I suspect if we knew what the blood pressure level was 24 hours a day including the overshoots of very high pressure, we might be in a better position to evaluate this point. But I do not like to see patients remain with a high blood pressure although some of them may live to be 80 years old and may finally be run over by an automobile. They are not good insurance risks. I think the pressure should be reduced, if possible.

DR. LIKOFF: This is a very simple and almost homely comment to make under the circumstances. It has been emphasized during the last few moments that it is perfectly all right to employ all measures short of drug therapy in early hypertensives. At the same time there has been a very frank admission that such measures do not reduce blood pressure.

I believe the reason that we go along with this laissez-faire attitude is the fact that hypertension has a slow devolutionary process. The penalties for having hypertension which is not treated by drug therapy are not very great in many patients. This, therefore, is not a tribute to the success of a laissez-faire treatment but an acknowledgment that we can get away with it.

I would like to urge, and I know Dr. Wolferth in the past has urged, that a patient with early hypertension be considered an important medical problem, deserving of a definitive approach. Even though our approach from a drug standpoint may not be entirely what it is supposed to be, at least it may result in smaller morbidity than is commonly encountered.

MODERATOR HAFKENSCHIEL: Here is a question I shall direct to Dr. Clark. Of what value is chlorothiazide in the treatment of hypertension?

DR. CLARK: So far as my comments are concerned, they will have to be based on a consideration of the pharmacology of the drug rather than personal clinical experience. It is no surprise to me that chlorothiazide lowers blood pressure. We have all seen patients with hypertension who have had quite satisfactory lowerings of blood pressure on low-salt diets or following the use of other diuretic agents. Whether this is a matter of decrease in vascular reactivity as they are placed in negative sodium balance, or of contraction of total body fluids, more particularly extracellular fluid, or some other mechanism, is not clear. But the fact remains that a certain number of patients get blood pressure reductions from low-salt diets or other diuretics.

To me, the remarkable thing about chlorothiazide is not so much its effect upon blood pressure as that it seems likely to become an extraordinarily effective oral diuretic, because it inhibits the renal tubular reabsorption of both chloride and bicarbonate. Therefore, one can place patients on the drug and secure a substantially negative salt balance, without systemic acid-base disturbance. I believe the blood pressure effect is unquestionably secondary to this manifestation of drug action.

MODERATOR HAFKENSCHIEL: Is there any comment by any of the panelists who has had occasion to use chlorothiazide in his own practice?

DR. WOLFERTH: Chlorothiazide is, of course, a very new drug, and as Dr. Clark has pointed out, it has a new action. It is the first drug that has been used in the treatment of hypertension, as far as I know, which attacks it from any other than the neurogenic basis of hypertension. That statement may be open to challenge but

at least here is a drug that sweeps salt out of the body. We have felt that perhaps one of the reasons why adrenalectomy is effective in some people is because of its effect on salt metabolism and excretion. It has been extraordinarily interesting to me to observe that chlorothiazide has had its most sensational results, so far as my limited experience goes, in patients who have had sympathectomy. I have seen blood pressures which have not been anywhere near normal for ten years get back to normal, even to the point of the return of severe postural hypotension, which had been absent for that long period.

I believe that the current view is that in other types of hypertensive disease chlorothiazide is not particularly useful by itself but is useful in connection with other antihypertensive agents, notably the rauwolfia preparations. We have a lot to learn about it.

MODERATOR HAFKENSCHIEL: The next question I know from personal experience is very important, having seen a number of patients with severe diastolic hypertension whom I would categorize as being chronic alcoholics. This question I would like to direct to Dr. Weiss first.

Would you advise complete exclusion of alcohol in chronic hypertensives with no apparent symptoms, blood pressure over 200 systolic?

DR. WEISS: I cannot find any evidence that alcohol has anything to do with hypertension. It is conceivable that the same thing that makes a person hypertensive also makes him alcoholic. You prefaced the statement with the remark that you were talking about a chronic alcoholic. Chronic alcoholism would certainly add to the difficulties of controlling hypertension. On the other hand, a patient with hypertension may consume a little alcohol without damage to his cardiovascular renal system.

May I, while speaking, refer to a previous statement because I may not get another chance to talk. I object to Dr. Likoff's suggestion that if you do not use antihypertensive drugs you have a laissez-faire method of approach to early hypertension. I do not believe that for a moment. I think that the psychosomatic approach to hypertension is a dynamic approach, and it does not exclude the use of drugs. But I am objecting to the use of the more potent drugs in the treatment of early or mild hypertension. I am waiting for a demonstration that their benefits outweigh their disadvantages.

MODERATOR HAFKENSCHIEL: Dr. Likoff, would you like to make a short rebuttal now?

DR. LIKOFF: I would just correct one term in Dr. Weiss' quote. I said that the approach, without drugs, to the problem of hypertension was a laissez-faire attitude. In short, nothing that I know of, other than drugs, actually reduces blood pressure. I full well realize that an elevated blood pressure is only a small part of the disease.

MODERATOR HAFKENSCHIEL: Here is a question for Dr. Clark. Should hypertensives be accepted as blood donors?

DR. CLARK: I do not know of any reason why they should not. Of course, one must hedge that with all sorts of ifs, ands, and buts—the degree, the severity, and nature of the hypertension. Ordinarily, there is no reason why they shouldn't.

MODERATOR HAFKENSCHIEL: Dr. Clark, would you discuss the treatment of anemia in patients with hypertension, particularly those with renal disease? Are there any tricks in treating such patients?

DR. CLARK: I can answer that quite easily. It is extraordinarily unsatisfactory, and I think you should not play for too large gains. If one wishes to bring a hemoglobin of, say, 8 g, up to 10 or 12 g, this is best accomplished by transfusions of packed red cells. Let me caution against the transfusion of whole blood, even in small amounts, in these patients, because expansion of their intravascular volume very promptly leads to pulmonary edema and serious troubles.

SUMMARY

MODERATOR HAFKENSCHIEL: This seems to be an appropriate time to stop and sum up and emphasize a few of the important points in the day-to-day management of patients with high blood pressure. I have asked Dr. Wolferth to be prepared to do this because of his long experience as a clinician and a teacher.

This latter period began in 1920 when he returned from service in France and England in World War I and rejoined the faculty of the University of Pennsylvania as Associate in Medicine. I am happy to say he continues to teach in the University Hospital to the present day, even though he has been emeritus for four years.

DR. WOLFERTH: I have been rather pleasantly surprised or astonished, if that is the word, this afternoon to find that our areas of disagreement were far less than I had anticipated. I am sure we all are impressed by the importance of the psychogenic aspects of blood pressure and the value of paying attention to such matters in the treatment of our patients. There are other factors concerned in hypertension that must be considered, and these have been very well brought out especially by Dr. Clark's discussion of the role of the kidneys. I think he has brought us up-to-date in that field.

How are we going to make further progress? I believe that the neurophysiologists will help us as time goes on. The endocrinologists may help us to attain some breakthroughs that we very urgently need. We need much more information. If we have to place 85 per cent of our patients in the grabbag of essential hypertension, which means hypertension the etiology of which we do not know, then we have not made satisfactory progress in the study of the etiology of this disorder.

You have noticed this afternoon that all of us in our discussions of treatment have been groping for etiologic factors, be they psychogenic, neurogenic, or humoral. Recent progress in the finding of disturbances of arterial blood supply to the kidney, for which Goldblatt had prepared us long ago, has taken a few cases out of the grabbag. There is other work going on that has exciting possibilities. What about the roles of norepinephrine, and serotonin in central nervous system tissues? What help are we going to get there?

We have made great progress in drug therapy, despite the differences of opinion that have appeared here. The newest of these drugs as of today is chlorothiazide. The future looks bright. I think the problems of hypertensive disease are on the way to solution, but there is still a great deal of work that needs to be done.

Historical Milestones

Mountain Sickness as Described by Fray Joseph De Acosta, 1589

SAUL JARCHO, M.D.

New York, New York

THE DISCOVERY of the New World introduced Europeans to new peoples, new animals, new plants, and new geographical features. Each of these new elements was to leave its imprint on the newly developing medicine of the Renaissance. The plants, for example, are recorded in the writings of Francisco Hernández[1] (1517–87) and Nicolas Monardes[2] (1493–1588). The mountains, by reason of their altitude alone, could not fail to impress European newcomers to the New World, since the higher mountains of Asia were not yet generally known and the tallest peaks of the Alps were all less than 16,000 feet high, whereas in the new domains in South America men found at least 50 peaks which exceed 20,000 feet. The exploration of these high ranges inevitably led to the recognition of altitude sickness.

Joseph de Acosta (1539–99), the courageous and intelligent man whose observations are to be reprinted here, was a Spanish Jesuit who went to Peru in 1571. Sixteen years later he returned to Europe, and spent his remaining 12 years in religious, literary, and educational work. At the time of his death, in 1599, he was rector of the University of Salamanca.

His book appeared first in Latin, in 1589, and was published in Salamanca under the title of *De natura novi orbis*. The first of numerous Spanish editions was published in Seville in 1590 with the title *Historia Natural y Moral de las Indias*. The following excerpt is freely translated from a reprint of the 1590 edition.[3]

ACOSTA'S DESCRIPTION

In Peru there is an extremely high mountain range called Pariacaca. I had heard tell of the effects which it causes and I went prepared as well as I could, complying with the advice given in that region by those who are called *vaquianos* or guides. Yet despite all my preparation, when I went up what are called "the stairs" —the highest part of the range—almost immediately I suffered anguish so severe that I had the idea of throwing myself from the cavalcade on to the ground. Although there were many of us travelling together, each one was forcing his speed without waiting for anyone else, in order to get out of that evil place. Accordingly I found myself left alone with one Indian, whom I asked to help me stay on my horse. At the same time I retched and vomited so violently that I thought I was dying, because after throwing up food and phlegm, then bile and more bile, some yellow and some green, I finally vomited blood, on account of the violence which my stomach was suffering. If this had lasted I should certainly have perished, but it did not continue for more than three or four hours, until we had descended a considerable distance and arrived at a more suitable climate. All my 14 or 15 travelling companions were exhausted. Some were seeking confession, as they really thought they were dying. Others dismounted and were overcome by vomiting and diarrhea; and I was told that some people had lost their lives. I saw one man who had thrown himself on the ground and was screaming from the intense pain which the passage of Pariacaca had caused. But ordinarily it causes no great harm except the weariness and grievous disgust which prevails while the crossing lasts. And it is not just that Pariacaca

pass which produces this effect but that entire range of mountains, which runs for more than 500 leagues. Wherever anyone crosses it he feels that disorder, although more in some parts of the range than in others, and most of all among those people who climb from the seacoast to the mountains, and not in those who descend from the mountains to the plains . . . In that region I always suffered the changes and dizziness that I have mentioned although never as severely as happened the first time at Pariacaca. Everyone else who has tried it has had the same experience.

There is no doubt whatever that the cause of that strange disorder and alteration is the wind or atmosphere that prevails there, because the only treatment found (and it is a very good one) consists in covering the ears, nose and mouth as well as possible, and in clothing oneself well, especially over the abdomen. The air is so fine and penetrating that it enters the intestines. Not only do human beings suffer this oppression, but animals do also; at times they become so quiet that no spur is able to move them.

In my opinion this region is one of the highest on earth. It rises to an immense distance and it seems to me that the snow-covered peaks in Spain and the Pyrenees and the Italian Alps are merely like ordinary houses compared to tall towers. Hence, I am convinced that the element of air in the region of Pariacaca is so subtle and delicate that it is unsuitable for human respiration, which requires thicker and more tempered air. This I think is the reason the stomach becomes so violently disturbed and the victim completely prostrated.

The snowy mountains or ranges of Europe which I have seen have cold air which is annoying and makes a person cover up well; the cold does not take away the appetite but on the contrary rouses it. It causes pain in the feet and hands but not vomiting or retching. Moreover, it acts externally. The cold of the Indies, which I have mentioned, turns over the intestines but causes no annoyance of the hands and feet or any external part. Even more astonishing is the fact that in this region the sun and heat are very moderate. Therefore, I believe that the harm comes from the quality of the air which is inspired and respired; it is extremely fine and delicate and its cold is not so much sensible as penetrative.

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Calcific Aortic Stenosis vs. Syphilitic Aortic Insufficiency

Diagnostic Value of Intra-Aortic Pressure and Sound Tracings

HISTORY

This 69-year-old white female was admitted to the hospital because of a continuous, dull, aching pain in the mid-thoracic region and below the left scapula, of four weeks' duration. The pain radiated to both sides of the anterior chest wall and was more pronounced when she was reclining.

Her history dates back to 1929, when pernicious anemia was discovered. This was treated with injections of refined liver, with complete remission. She had been followed in the Cardiac Clinic since 1949 with the complaint of precordial pain on exertion, promptly relieved by nitroglycerin. In addition, liver injections were continued. In 1955, she was placed on digitalis and low salt diet because of minimal evidence of left heart failure. There was history of moderate hypertension, at least since 1950, but no history of rheumatic fever or lues.

PHYSICAL EXAMINATION

Physical examination revealed a pale, slightly orthopneic, elderly, white female. The blood pressure was 140/58 and the pulse was 80 and regular. The apical impulse was diffusely palpable in the 5th and 6th left interspaces at the midclavicular line. There was a harsh, grade III, aortic systolic murmur transmitted to the neck, and a grade II, blowing, aortic diastolic murmur. The 2nd aortic sound was diminished. The liver edge was barely palpable below the right costal margin and was tender. *A large pulsating mass* was detected in the left upper quadrant of the abdomen, just lateral to the midline. The femoral pulses were present. There was no peripheral edema.

LABORATORY FINDINGS

Significant laboratory tests included persistently negative serological tests for syphilis, including a negative complement fixation. Hemoglobin was 12.9 grams and the hematocrit was 40 per cent. Blood glucose was 133 and blood urea nitrogen was 37 mg %. Urinalysis was essentially negative, except for a trace of protein and an occasional hyaline cast.

X-RAY EXAMINATION

The x-rays revealed in 1950 a widened ascending aorta, and a progressive increase in size of this vessel until 1958. Fluoroscopy (1958) revealed that the lower portion of this bulging area pulsated synchronously with the heart, whereas the pulsations in the upper portion were diminished. A large linear calcification was visible in the upper pole of this mass. The trachea was displaced to the right. X-rays of the abdomen in 1956 and 1957 revealed a calcified aneurysmal dilatation of the abdominal aorta.

ELECTROCARDIOGRAM

The record showed evidence of left ventricu-

Fig. 1. Intra-aortic tracing of pressure (below) and sound (above), simultaneous with electrocardiogram. At left, slow speed; at right, high speed. Several notchings indicate turbulence of flow caused by stenosis (arrows). Diamond-shaped systolic murmur and small 2nd sound within the aorta, characteristic of aortic stenosis.

lar hypertrophy and strain, intraventricular block, and myocardial ischemia.

PHONOCARDIOGRAM

Diamond-shaped systolic murmur over aortic area followed by a small, delayed second sound (paradoxical splitting). Small, early diastolic aortic murmur.

Diagnosis

At this point, two alternative diagnoses were discussed: (1) Syphilitic aortitis with aortic aneurysms; aortic insufficiency and "relative" stenosis; or (2) atherosclerotic lesions of the aorta with formation of aneurysms; calcific aortic stenosis, aortic insufficiency.

The occurrence of a delayed aortic component of the second sound, causing a "paradoxical splitting" was interpreted as due to organic aortic stenosis. However, final proof was missing. Therefore, aortic catheterization was done through a brachial artery.

The aortic pressure tracing (Fig. 1) revealed a slowly rising pulse with small notchings, indicating the turbulence of flow. A sound tracing recorded within the aorta (Fig. 1) revealed a series of large vibrations coinciding with the rise of the pulse.

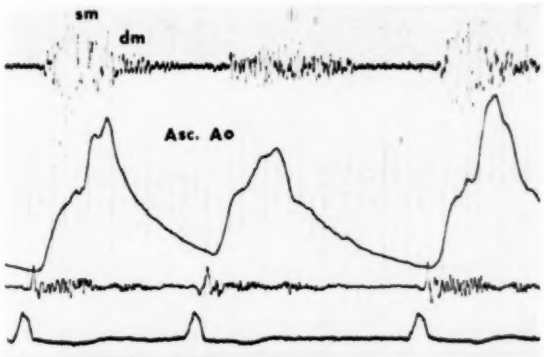

Fig. 2. For comparison, similar tracings from a case with severe obstructive stenosis of the aorta are presented.

The above data were interpreted as confirming the existence of moderate aortic stenosis. The determination of a gradient across the aortic valve was not done as no left ventricular catheterization was considered. Simultaneous left ventricular and aortic measurements of pressure would have given the final proof of the stenosis.

The above interpretation was subsequently confirmed by a negative Treponema pallidum immobilization test.

A. A. Luisada, M.D.
S. Fishkin, M.D.
Chicago, Illinois

Readers are invited to submit reports of interesting cases and illustrative tracings for this department. These should not exceed 1,000 words in length. Although not necessarily original all material submitted should have teaching value.

Progress Notes in Cardiology

Edited by EMANUEL GOLDBERGER, M.D., F.A.C.C.

New York, New York

Investigators and research workers are invited to submit, with a view to publication in an early issue, résumés of work in progress or recently completed.

The Treatment of Complete Heart Block by the Use of an Artificial Pacemaker and a Myocardial Electrode

ONE of the serious complications of surgical procedures for repairing atrial and ventricular septal defects has been the occurrence of postoperative complete A-V heart block. Patients with this complication die often in the immediate postoperative period of low-output heart failure when the heart rate falls too low.

Although isuprel, given intravenously, reduces the mortality rate in these patients with postoperative complete heart block to 50 per cent, the response of individual patients to this medication is unpredictable. Because of this, a more reliable method of electrical stimulation of the ventricles was sought for and developed by Drs. William L. Weirich (University of California Medical Center, San Francisco) and Matthias Paneth, V. L. Gott, and C. Walton Lillehei (University of Minnesota, Minneapolis).

Experimental Studies: These investigators produced complete heart block in 50 mongrel dogs by placing a ligature around the right and left bundle branches during inflow stasis. A fine insulated wire was inserted subepicardially in the wall of the right ventricle and was connected to an electrical pacemaker. The electrical circuit was completed by placing a flat indifferent electrode, 1–2 cm in diameter, on or under the skin over the apex beat of the heart. Complete control of the ventricular rate was achieved with low currents (5–45 milliamperes). There were no instances of ventricular escape or fibrillation, and the tissue reaction about the electrodes was insignificant. The electrodes were removed without complications by simple traction at the completion of the studies.

Systemic arterial pressure and cardiac output were measured in 13 animals prior to, following the production of heart block, and during electrical stimulation at various rates. Mean systemic arterial pressure diminished to 70 per cent of pre-block levels and was restored to control values during electrical stimulation of the ventricles. When complete heart block was produced, the cardiac output diminished to approximately 55 per cent of control measurements. Electrical stimulation of the ventricles resulted in an increase of cardiac output from 72 to 167 per cent of control values. A pacemaker rate of 90 per min more closely approximated the control pressure and output in spite of the fact that the pre-block rates were usually higher.

Clinical Application: This method of controlling the heart rate during complete heart block resulting from intracardiac surgical procedures has been used successfully by them in 34 patients. One death occurred early in the series when the skin electrode was dislodged. The indifferent electrode is implanted subcutaneously now, and this complication has not recurred. One patient's heart was stimulated for 21 consecutive days. The patients have had no discomfort from the electrical impulses and no complications have been observed from removal of the myocardial electrode. Isuprel in doses of 2.5 mg administered rectally every hour has been used often during electrical stim-

ulation of the heart for the drug's positive inotropic effect.

At the present time, a small transistorized, battery operated pacemaker is being used effectively. Any commercially available pacemaker that is calibrated accurately to deliver low voltages (0–5 v) may be used, such as the *Morris Clinical Pacemaker, model p2A*, made by Levinthal Electronic Products, Inc., Palo Alto, California.

Pacemaker stimulation is stopped: (1) when the patient resumes a sinus rhythm which is determined clinically and by electrocardiography; and (2) when the patient remains in complete heart block after the 10–14th day, the pacemaker may be turned off if the patient's heart rate is maintained at an adequate level by the use of isuprel (2.5–10 mg given rectally every one to three hours).

Closed Chest Defibrillation of the Heart

THE most reliable and effective method of arresting ventricular fibrillation is to send sufficient electric current through the heart to depolarize the cardiac fibres and bring them to a uniform state of rest. Electrodes of the correct size, properly located on the surface of the chest, and supplied with current from a suitable source may be used to send the desired current through the heart, thereby eliminating the necessity of thoracotomy. Such an apparatus has been developed by Drs. W. B. Kouwenhoven, W. R. Milnor, G. G. Knickerbocker and William R. Chesnut (Schools of Engineering and Medicine, The Johns Hopkins University) (Surgery, 42: 550, 1957).

The electrodes, of sheet copper—8.5 cm in diameter—are mounted on plastic discs attached to concentric handles so that they may be easily held by the doctor. Plastic guards are provided which prevent the user's hands from coming into contact with either the skin of the patient or the circuit. The electrodes, greased with electrocardiograph electrode jelly, are pressed against the surface of the chest with a force of 4 to 5 kg. This insures good electrical contact and prevents burning the skin. One electrode is placed on the suprasternal notch and the other at the level of the xiphoid on the left midclavicular line.

Ordinary 120 v. alternating current was found to be an effective and reliable source of electrical energy for defibrillation. It requires a current of about five amperes. In order to drive this current through the human chest, an open circuit voltage of 480 v is applied to the electrodes. A one to four step-up three KVA transformer is used to increase the 120 v supply to the desired voltage.

The alternating current is sent through the patient's chest for one-fourth of a second. This duration is controlled by a clock timer which is actuated by a foot switch. The equipment is mounted on a small movable table.

When ventricular fibrillation occurs, the equipment is brought in and connected to an electric outlet. The foot switch is placed on the floor convenient to the operator, who takes the greased electrodes, places them on the chest and rubs in the jelly. Then with a firm pressure, he steps on the foot switch and sends a single pulse of alternating current through the patient's chest for one-fourth of a second. This should arrest the fibrillation. If it fails to do so, a second application may be given about 15 sec later.

If the defibrillating current is applied within two minutes or less after the onset of fibrillation, the human heart usually will resume normal sinus rhythm spontaneously. If the heart remains in standstill because of anoxia, an artificial pacemaker should be tried to produce effective contractions.

The above method has been used in human hearts more than one hundred times without a single failure. No evidence has been found that its use has resulted in any trauma.

Cardiac Resuscitation

Edited by PALUEL J. FLAGG, M.D., F.A.C.C.*

New York, New York

A Total Approach to the Problem of Hypoxia

A Knowledge of the Behavior and Use of Oxygen

SINCE hypoxia is due to a reduction in the normal tissue oxygen and since this fact constitutes the basis of the total problem, its relief depends upon a knowledge of the behavior and the technics of the use of this gas.

In order to understand the behavior of oxygen, it is necessary to consider it in its relation to other gases, such as carbon dioxide and nitrogen. A brief look at the physics and the physiology in which gases play their part finds us faced with a new and important science, the use of gases for medical purposes, or the science of pneumatology. The scope of this science parallels that of the science of the use of drugs, or pharmacology. As a science, the knowledge of gas-therapy or pneumatology is wider in its application than is the field of any medical specialty. Consequently, pneumatology cannot be contained within a specialty. It is for the use of everybody in accordance with the capacity to understand the principles involved, and in accordance with the laws restricting the technics of its use, as set up by the various medical specialties.

SUMMARY OF THE PHYSICAL PROPERTIES OF OXYGEN

ELASTICITY

While a tabulation of facts has the virtue of compact conciseness, like a kit of tools, it has little else. A tabulation is merely a list of familiar ideas. A refresher, on the other hand, attempts to make each fact sufficiently interesting to invite and to hold attention. For example, a gas, as oxygen, is elastic. If the atmospheric pressure which surrounds it is reduced, it expands. For instance, if one takes off in a plane, let us say at Idlewild at the level of the Atlantic Ocean, where the pressure is about 760 mm, when he gets up to the cruising range, presumably 18,000 feet, gases inside and outside of him expand to twice their volume by virtue of their *elasticity*. This would be pretty uncomfortable if the plane were not pressurized to 5,000 or 8,000 feet of altitude, so that it is tolerable, unless to begin with one is troubled with flatulence.

DIFFUSIBILITY

The elasticity of oxygen is common to any other gas with which it happens to be mixed or diffused. However, the tendency to diffuse is different from that of nitrogen, for example. This difference is due to the activity of its molecules. This tendency to diffuse creates a particular pressure within the total pressure of the gas mixture. This particular, or *partial pressure*, always remains the same. The pressure of oxygen in the atmosphere is less than that of nitrogen. This is clear when we analyze the atmosphere and note that the partial pressure of

* President, National Resuscitation Society, Inc.

oxygen is only about 20 per cent and that of nitrogen 80 per cent. If one cares to bother about the partial pressure, in actual millimeters of mercury, he will find that the pressure of oxygen is only 152 mm of the total 760 mm pressure.

As we can carry on under ordinary conditions with oxygen concentrations of as little as 13 per cent in the air we breathe, we are not much interested until we face an acute respirocardiac failure which may call for as high a concentration as possible, because of new factors affecting its diffusion.

While the diffusibility of O_2 is of great concern in flight, diffusibility operates on land as well. In an open, unrestricted atmosphere diffusibility establishes an equilibrium based upon the partial pressure common to O_2, provided that there is enough O_2 present to establish this level. In a closed atmosphere of decaying fruit for example, in a manhole or in a declivity, the O_2 may be so scarce as to be far below its partial pressure. The result of an exposure to such conditions is a fatal anoxic anoxia. On the other hand, O_2 may be highly concentrated in a restricted space as in the pharynx by a nasal catheter or in an inhaler.

It is to be pointed out that while partial pressure and percentage by volume are the same thing, as far as the behavior of gases is concerned, this is not the same as it pertains to the effect produced in the blood and tissues. Here enter other factors, notably that of solubility, as for example the predilection of hemoglobin for oxygen or the almost magnet-like attraction to carbon monoxide.

SOLUBILITY

Oxygen has a specific measure (coefficient) of solubility in fluid plasma which is quite separate from its union with the hemoglobin. The actual amount of oxygen that can be dissolved in the plasma of a subject depends upon its solubility, the total weight of the subject, and the concentration of the O_2 administered.

Fortunately the solubility of a gas in the plasma is determined by its partial pressure. The presence of one gas in solution does not influence the entrance of another. On the other hand, once equilibrium has been secured no more gas can be absorbed. Incidentally, this fact has a bearing upon the safety of the gaseous anesthetics as compared to anesthesia effected by drugs. For example, when ether is administered, once the desired level has been secured, an equilibrium is established. This may be maintained as long as desired without cumulative effects (except for fat and bone saturation).

Biochemical Properties of Oxygen

The question now arises, how does oxygen in the ambient (surrounding) atmosphere get into the tissue cell? Here we face the facts set forth in Figure 1. These facts move from the physical to the biochemical, from external to internal respiration.

EXTERNAL RESPIRATION

We observe that the respiratory rate varies from 15 to 40 *l*/min. Rhythm is, in part, controlled by the expansion and contraction of the alveoli, activated by the Hering-Breuer reflex. The ordinary amount of air breathed is about 500 ml. The amount of air that can be forcefully exhaled after the ordinary expiration, 1,000 ml, contains about 17 per cent oxygen. The amount of air that can be "breathed in" following an ordinary inspiration is about 2,500 ml. The enormous alveolar surface for gas diffusion and solution is amazing, for it equals the inside of a balloon 20 feet in diameter. Assuming that the circulation, muscle tone, and cell metabolism operate normally, nature has provided a tremendous margin of safety for ordinary stress and strain. However, we are geared for increased exertion rather than for inaction. We can breathe 40 *l* of air/min for a long time, but everything tends to fall apart if we breathe 2 *l*/min for a long time. While external respiration is familiar, it is not as important as internal respiration. Here, gases dissolving in the fluid plasma, red blood and tissue cells, carry on their selective biochemical metabolism. Here the amount the oxygen and CO_2 in solution, determined by the partial pressure, governs the rate, rhythm, and amplitude of the respiration with a delicacy so sensitive as to react to variations of carbon dioxide, during inspiration and expiration.

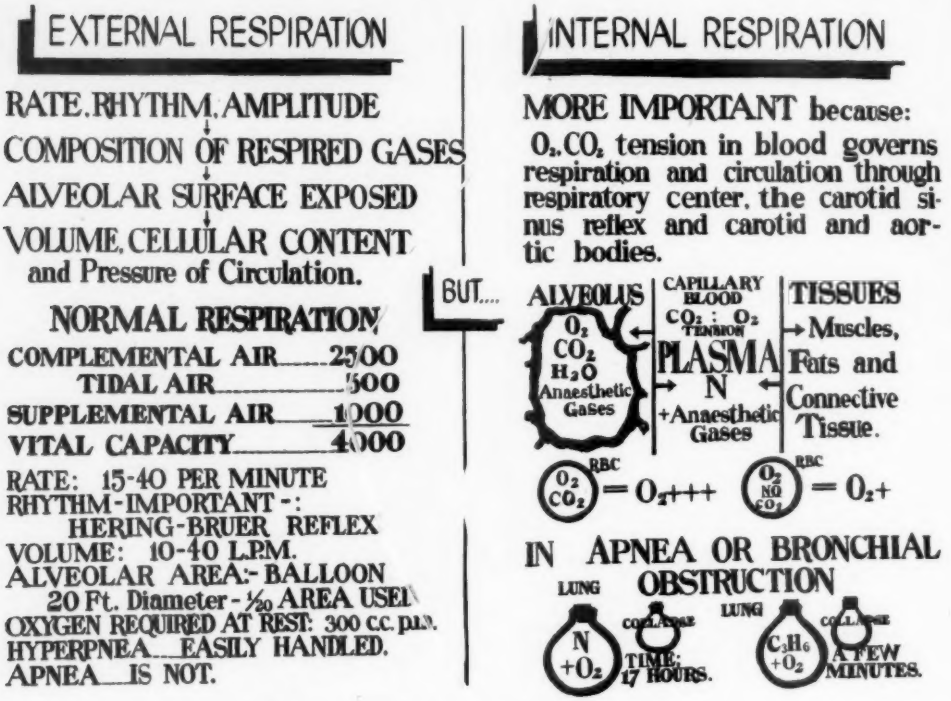

Fig. 1. External and Internal respiration.

INTERNAL RESPIRATION

Oxygen and carbon dioxide move from the alveoli in and out of the capillaries in accordance with the law of diffusion, seeking a level in equilibrium. The same action takes place when the blood in the capillaries comes in contact with the tissue cells. During the release of oxygen from the hemoglobin, a curious biochemical phenomenon is observed. If the CO_2 in the plasma is reduced below normal, the hemoglobin does release its oxygen (Bohr phenomenon). This fact is to be kept in mind whenever the patient overbreathes from any cause.

Nitrogen: What about the nitrogen which makes up 80 per cent of the air we breathe, isn't this important? It certainly is and its importance also turns upon problems of diffusion. Nitrogen provides the solid background, the vehicle, as it were, for the conveyance of other gases. The safety factor which it provides is due to the fact that our blood and tissues are already 80% saturated with nitrogen, through the partial pressure of diffusion. Air respired enters the alveoli as 80 per cent nitrogen, 20 per cent oxygen, and small percentages of CO_2 and water vapor. Every gas but nitrogen is in constant passage in and out of the alveolar capillaries. Nitrogen is stationary because the tissues and blood are already saturated with it. It alone is in equilibrium. As a consequence, should a bronchus be shut off, the air in the obstructed lobe or lobule remains for a long time (15 to 17 hours) before the lung collapses. On the other hand, suppose the lungs are filled with some other gas and the breathing stops, the blood circulating in the alveolar capillaries picks up this gas at a speed depending upon the difference in concentration in the alveoli and the blood. During anesthesia, when apnea is permitted and the lungs are filled with an anesthetic gas, without nitrogen to act as a buffer, prompt atelectasis or collapse of the lung may occur. The answer to this hazard is to prevent apnea and to fill the lungs frequently with air.

Under exceptional circumstances, as in high altitude flying or submarine escape, the friendly buffer, nitrogen, becomes a liability. In the rarefied high altitude with its reduced pressure, the nitrogen in the blood and tissues, under greater pressure, strives to escape as in effervescent soda, and to establish its normal equilibrium. Bubbles of gas form in the tissues and give

rise to the "bends" or aeroembolism. There are two ways to meet this hazard, first, by increasing the ambient (surrounding) atmospheric pressure in a pressure chamber, second, by removing some of the nitrogen by placing the subject for some time in an oxygen atmosphere, before flight or immersion (surfacing). Oxygen by displacing a portion of the nitrogen decreases the degree of aeroembolism.

Applications of Pneumatology

The foregoing simple physical and physiologic facts stress the science of pneumatology in its treatment of respirocardiac failure. Popularization of this science is therefore suggested as the best means of meeting the total problem of hypoxia. Everybody, certainly every physician, should be perfectly familiar with elasticity, diffusion, and solubility and react spontaneously to this normal behavior of oxygen.

It is to be repeated, again and again, that pneumatology is a *science. It is not a medical specialty.* It provides the therapeutic agents for many professional and technical groups in the medical field, including the physician, the dentist, the technician in anesthesia, inhalation therapy, and resuscitation. Integration of these groups would be immensely helpful. It would constitute a realistic anti-death movement. How can such integration be sparked? As a starter, someone should come up with a text on the "Science of Pneumatology."

Coming Articles in this Series

This is the third of a series of articles on Acute Respirocardiac Failure, presently appearing in The American Journal of Cardiology. In accordance with the nature of the problem Respiratory Resuscitation is receiving first consideration. The September Issue of the Journal will feature the Doctrine of Hypoxia. This will be followed by Long-Range Indoctrination, Immediate Indoctrination and finally in the December Issue, by an article "Man in Vivo," a three dimensional view, stressing the integration of form, function, and timing in its application to the respirocardiovascular system.

Note: Reprints of the current article are mailed each month to the membership of the National Resuscitation Society.

All professional and technical individuals and groups employing gases for therapeutic purposes are eligible for membership. For information address Secretary, National Resuscitation Society, Inc., 2 East 63rd Street, New York 21, N. Y.

Workmen's Compensation for the Cardiac

Workmen's Compensation Committee of the American College of Cardiology

Summary of Proceedings of the Third Meeting

THE Committee held its third meeting during the Seventh Annual Convention of the American College of Cardiology in St. Louis on May 22, 1958. Dr. Louis H. Sigler, Chairman of the Committee, presided.

The following other members attended:

Arthur Bernstein, *Newark, N. J.*
Jerome W. Bodlander, *Los Angeles, Cal.*
Simon Dack, *New York, N. Y.*
Herbert Eichert, *Miami, Fla.*
Ronald L. Hamilton, *Binghamton, N. Y.*
Ernst Jokl, *Lexington, Ky.*
G. W. H. Schepers, *Ann Arbor, Mich.*
John R. Williams, *Rochester, N. Y.*

Case Presentation: The first part of the committee's deliberations was devoted to a discussion of a recent New York State compensation claim preferred by the estate of a workman who had died from cardiovascular causes.*

The case concerned a man 50 years of age who had been known to suffer from general arteriosclerosis and hypertension. While standing on a ladder and painting a ceiling, he fell and suffered a blunt concussion injury to the chest. On admission to the hospital evidence of a posterior myocardial infarct was obtained. He returned to work six months later and while lifting a heavy weight he suffered an attack of left heart failure. From then on he was totally incapacitated. Progressive cardiac failure ensued, followed by hemiplegia and death after four years. Autopsy revealed marked generalized arteriosclerosis. The heart weighed 580 grams. The right coronary artery contained an organized thrombosis and there was infarction of the posterior wall of the left ventricle extending to a fourth of the adjacent interventricular septum. There was extensive softening of the left cerebral hemisphere due to advanced cerebral arteriosclerosis.

Cardiac Trauma?: Dr. Sigler brought up the question as to whether the fall and hitting of the chest were competent producing causes of the acute cardiac injury. He quoted part of a letter received from Dr. Ray W. Kissane, one of the committee members absent, who referred to his original work on traumatic heart disease in dogs. One of 20 animals subjected to blows developed a thrombus of a coronary vessel with myocardial infarction. He did not believe, however, that the fall in the case presented for discussion produced the coronary thrombosis. Dr. Schepers drew attention to the fact that essential anatomic differences exist between the intrathoracic topography of the human and the canine heart, in that the coronary arteries of the latter are situated laterally while in the human heart the left branch of the coronary artery faces the anterior wall. Dr. Sigler mentioned a cardiac study on 42 patients he had reported in 1945 in the American Heart Journal, all of whom had sustained severe bodily injuries in various accidents. About 76 per cent of these patients showed clinical and/or electrocardiographic evidence of heart damage. He observed that cardiac injury is frequently overlooked since the condition is commonly but one of other extensive injuries suffered by the patient. Dr. Schepers suggested that the committee go on record in recommend-

* For the complete case history and medico-legal questions related thereto, see AM. J. CARDIOL. 2: 123, 1958.

ing that every patient treated for multiple injuries be examined electrocardiographically, and that the possibility of a commotio cordis being present always be kept in mind in such cases.

Dr. Bodlander referred to a case of anterior myocardial infarction in a football player. Dr. Jokl reported six cases of commotio cordis in boxers, two of them fatal.

Factor of Strain: Dr. Sigler pointed out the possibility that the coronary occlusion occurred in the patient under discussion while he was standing on the ladder during the painting job, stretching and straining himself. This might have caused fainting and the fall off the ladder. Dr. Bernstein likewise felt that the effort alone could have caused the thrombosis. The thrombotic lesion in the coronary artery might have been due to the fact that he "strained" himself while painting and that he thus lost consciousness and fell.

Dr. Jokl pointed out that exercise *per se* will never cause intravascular thrombosis and that the presence of lesions of the intima or of other pathologic changes is a prerequisite for such occurrences. He cited several cases of sportsmen in whom intravascular thrombi had formed in association with effort. In all these cases preexisting lesions could subsequently be demonstrated. Conversely, he reminded the committee that outstanding athletes do not develop thrombosis after the most extraordinary physical exertions.

Coronary Spasm?: Dr. Williams asked whether arteriospasms can cause the clinical signs and symptoms of coronary occlusion. Dr. Schepers replied in the affirmative, detailing a number of observations, e.g., coronary spasm following acute gallbladder pathology; injury to the left arm; and evidence obtained in animal studies in which crushing of a foot was followed immediately by reflex contractions of the coronary artery tree.

Dr. Eichert stressed the difficulty of the differential diagnosis between coronary artery spasm and thrombosis, emphasizing the significance of cases of death due to angina pectoris in which autopsy fails to demonstrate occluding lesions. Dr. Hamilton referred to spasm of retinal arteries where direct observation is at times possible. Dr. Sigler spoke of a possible causative role played by the release into the blood stream of sympathicomimetic substances associated with strain. The presence of RS-T segment depression occurring on strain is considered to be evidence of myocardial ischemia due to transient coronary artery insufficiency. Dr. Bernstein and Dr. Bodlander doubted whether minor changes of the RS-T segment in the electrocardiogram can as such be considered convincing proof of coronary spasm.

Does Coronary Disease Produce Myocardial Hypertrophy?: Dr. Sigler brought up the question as to whether or not the pre-existing myocardial infarction in this case, caused by the accident, was one of the causes of the cardiac hypertrophy observed on postmortem examination or whether the hypertrophy was due solely to the underlying hypertension. Opinions were divided on the question as to whether pre-existing myocardial infarction can cause cardiac hypertrophy. Dr. Jokl pointed out that in the majority of cases of death from chronic coronary disease the hearts are found at autopsy to be of normal or even of small size. Dr. Schepers and Dr. Dack concurred, adding that the situation is different if arterial hypertension is present at the same time. Dr. Williams wanted to know whether the size of myocardial fibers in cardiac regions that are affected by the coronary occlusion has been compared with that in other parts of the heart. He stated that it is quite possible that a differential pattern of atrophic and hypertrophic fiber assemblages may exist side by side. Dr. Sigler stated that in his opinion if a large area of the heart is devitalized to a great extent by a large organized infarct, the remaining normal heart muscle must carry the greater brunt of the contraction and may conceivably be expected to undergo some hypertrophy, particularly in the presence of increased peripheral resistance in hypertension. He cited an example of that kind in a male with considerable cardiac hypertrophy in the presence of a long-standing organized infarct, in the absence of hypertension. He felt that the question certainly needs further study. In his letter Dr. Kissane expressed a similar opinion on this question.

Was Original Trauma Responsible for Subsequent Death?: Dr. Sigler brought up the question as to whether the original trauma in the case under

consideration was one of the causes of the final death of the patient, or was death due solely to the progressive general arteriosclerosis and hypertension. Dr. Eichert stressed that the history of the patient under discussion is typical of progressive systemic arteriosclerosis, and that the trauma can therefore not be considered a cause of the death. Dr. Dack agreed, saying that a healed infarction as such no longer constitutes a hazard to life. However, he was not prepared to dismiss the possibility of a traumatic aggravation of the pre-existing cardiac lesion. Dr. Schepers asked whether or not the decisive question in this case is: "Could the man have died from the original arteriosclerotic heart disease since he was known to be thus afflicted prior to the industrial accident?" The answer to this question is "yes."

Dr. Sigler reported that the Court ruled in favor of the deceased's estate, recognizing the industrial accident and the stress of the subsequent occupational activity as contributory causes of the total disablement and death.

Plan of Future Studies

The question was then discussed as to how to proceed in our future studies of the problem of cardiac disability in relation to strain, effort, and trauma. Dr. Schepers moved that the committee proceed with the allocation of study subjects to be accepted by members of the committee so as to comply with its long-term task of preparing a comprehensive statement of the various cardiovascular problems encountered in litigation in workmen's compensation cases.

The proposal, duly seconded, was accepted unanimously. The following assignments were agreed upon:

(1) Drs. Dill, Horvath, and Brofman: Dynamics of the circulation.

(2) Dr. Jokl: Cardiovascular adaptations to exercise and training, with special reference to the effect of prolonged inactivity and resumption of training thereafter.

(3) Dr. Hamilton: Stress in its relationship to blood lipids and intravascular coagulation.

(4) Dr. Eichert: The natural history of cardiovascular diseases.

(5) Dr. Dack: Longevity of cardiac patients, with special reference to coronary heart disease.

(6) Dr. Gelfand: Statistical data pertaining to cardiovascular diseases.

(7) Dr. Bernstein: The relationship between clinical and pathological findings in coronary heart disease.

(8) Dr. Kissane: Cardiac trauma.

(9) Dr. Schepers: Cardiovascular pathology.

(10) Dr. Williams: Disability schedules and their interpretation by Workmen's Compensation Boards in different states.

(11) Dr. Bodlander: Evaluation of cardiovascular evidence by Workmen's Compensation Courts in five Western states.

(12) Dr. Pollack: Relationship of physical activity to onset of symptoms of myocardial disease.

(13) Dr. Prinzmetal: Possible physical and emotional effects of strain on the coronary circulation and myocardium.

(14) Dr. Tandowsky: Causes, incidence, and outcome of cardiac disability in industry on the West Coast.

(15) Dr. Sigler: Correlation of the various studies.

Ernst Jokl, M.D., *Secretary*
University of Kentucky
Lexington, Ky.

College News

MEMORANDUM FOR ALL MEMBERS OF THE COLLEGE:

All too many applications for membership in the College are received incomplete. Applications require nominating letters from two members of the College giving their knowledge of the applicant in detail. Those members who sign applications guarantee to the College the desirability and qualifications of the applicant and hence are responsible after his acceptance for his value as a member. They should also see that every question is answered in the application and that photograph and other requirements are met. It has sometimes taken several months of correspondence to complete these details which sponsors had neglected. Please use the new forms.

Unless a man has a senior position in a hospital or medical school staff or has presented outstanding research reports the great majority of new applicants, with rare exception, should be recommended only for associate status.

The College is not making a drive for numerical strength but rather for men of recognized ability or who possess the potentiality of further development by training and experience in the College. Preferential consideration will be given to those who have passed their Internal Medicine or Speciality boards.

State or area governors and their deputies will investigate each applicant referred to them and certify to the requirements being met in all respects in order that the Credentials Committee has the best information available on which to pass judgment.

GEORGE W. CALVER, M.D.
President

Announcements

Third International Congress of Angiology

The Third International Congress of Angiology will be held in San Remo, Italy, September 24–28, 1958.

All inquiries pertaining to registration and the presentation of scientific papers should be addressed to The General Secretariat of the Congress, Clinica Dermatoligica, Universita, Pisa, Italy.

American Heart Association Scientific Sessions

A program that will emphasize the practical application by physicians of findings made through cardiovascular research is being planned for the 31st Annual Scientific Sessions of the American Heart Association to be held at the Civic Center, San Francisco, from October 24 through October 26, 1958. A section for scientific and commercial exhibits will be featured.

The American Society for the Study of Arteriosclerosis to Meet

The annual meeting of The American Society for the Study of Arteriosclerosis will take place October 24–26, 1958 at the Hotel Whitcomb, San Francisco, California.

Research Support

Applications by research investigators for support of studies to be developed during the fiscal year beginning July 1, 1959 are now being accepted by the American Heart Association. The deadlines for applications are: Research Fellowships and Established Investigatorships, September 15, 1958; Grants-in-Aid, November 1, 1958.

Information and application forms may be obtained from the Assistant Medical Director for Research, American Heart Association, 44 East 23rd Street, New York 10, N. Y.

Third World Congress of Cardiology

Brussels, September 14–21, 1958

OFFICE OF THE SECRETARY: 80, RUE MARCELIS, BRUSSELS

Program

Saturday, September 13

9 A.M.—Opening of the Secretary's office in Brussels University, 51 avenue Franklin Roosevelt

Sunday, September 14

2 P.M.—Official opening of the Technical Exhibition on the Congress premises

5 P.M.—Opening ceremony in the main room of the Palais des Beaux Arts, rue Ravenstein

8 P.M.—Reception at the Musées des Arts du Cinquantenaire, avenue des Nerviens

Monday, September 15, 9 to 11 A.M.

Symposia

CARDIAC ELECTRO-PHYSIOLOGY

C. Brooks, *Brooklyn;* H. Hecht, *Salt Lake City;* W. Mommaerts, *Los Angeles;* A. Rosenbleuth, *Mexico;* H. Schaefer, *Heidelberg.*

CORONARY CIRCULATION

D. E. Bedford, *London;* R. Froment, *Lyon;* D. E. Gregg, *Washington;* A. D. Morgan, *London;* H. Vastesaeger, *Brussels.*

ACQUIRED VALVULAR DISEASES

S. G. Blount, *Denver;* E. Coelho, *Lisbon;* J. Facquet, *Paris;* R. M. Harvey, *New York.*

RADIOLOGICAL METHODS

A. Castellanos, *Havana;* L. Condorelli, *Rome;* G. Dusaillant, *Santiago;* G. Giraud, *Montpelier;* C. Wegelius, *Rochester.*

Monday, September 15, 11:15 A.M.

General Conference

Chairman: I. CHÁVEZ, *Mexico*

Monday, September 15, 2 to 4 P.M.

Round Table Discussions

RHEUMATIC FEVER

E. G. L. Bywaters, *Maidenhead;* A. Cordeiro, *Lisbon;* R. Dubois, *Brussels;* J. D. Keith, *Toronto;* B. F. Massel, *Boston;* P. Mozzicoacci, *Paris;* V. Puddu, *Rome;* C. H. Rammelkamp, *Cleveland;* J. Roskam, *Liège.*

ANGINA PECTORIS AND MYOCARDIAL INFARCTION

E. C. Andrus, *Baltimore;* E. Doumer, *Lille;* J. S. LaDue, *New York;* A. Master, *New York;* A. Poppi, *Bologne;* J. J. Sampson, *San Francisco;* I. S. Wright, *New York.*

SURGERY OF ACQUIRED HEART DISEASE

C. Bailey, *Philadelphia;* F. D. Dodrill, *Detroit;* A. Dogliotti, *Turin;* L. B. Ellis, *Boston;* J. Govaerts, *Brussels;* C. W. Lillehei, *Minneapolis;* J. Mathey, *Paris;* T. H. Sellors, *London;* M. L. C. van Niewenhuysen, *Utrecht.*

ANGIOCARDIOGRAPHY

H. L. Abrams, *San Francisco;* P. F. Angelino, *Turin;* Bolt, *Cologne;* de Souza, *Lisbon;* Dorbecker, *Mexico;* C. T. Dotter, *Portland,* M. Mouquin, *Paris;* I. Steinberg, *New York.*

Tuesday, September 16, 9 to 11 A.M.

Symposia

PHYSIOLOGY OF THE CIRCULATION

Blumberger, *Aschaffenburg;* A. F. Cournand and H. W. Fritts, Jr., *New York;* H. W. Knipping, *Cologne;* W. F. Hamilton, *Augusta.*

NORMAL LIMITS AND FUNCTIONAL MODIFICATIONS OF THE ECG

M. Holzmann, *Zurich;* E. Lepeschkin, *Burlington;* A. Pick, *Chicago;* H. Reindell, *Freiburg;* R. F. Ziegler, *Detroit.*

PULMONARY CIRCULATION

H. Denolin, *Lyon;* H. Meesen, *Dusseldorf;* P. H. Rossier, *Zurich;* L. Scebat, *Paris;* P. Wood, *London.*

Tuesday, September 16, 11:45 A.M.

General Conference

Chairman: P. D. WHITE, *Boston*

Tuesday, September 16, 2 to 4 P.M.

Round Table Discussions

PHONOCARDIOGRAPHY

D. H. Bekkering, *La Haye;* K. Holldack, *Heidelberg;* C. Lian, *Paris;* A. A. Luisada, *Chicago;* P. Mounsey, *London;* V. A. McKusick, *Baltimore;* A. S. Nadas, *Boston.*

CLINICAL SIGNIFICANCE OF MINOR ELECTROCARDIOGRAPHIC ALTERATIONS

Arnolevitch, *Belgrade;* D. Durrer, *Amsterdam;* G. Frau, *Milan;* Plas, *Paris;* M. Prinzmetal, *Los Angeles;* P. Peuch, *Montpelier;* D. Sodi Pallares, *Mexico;* M. Sokolow, *San Francisco;* A. van Bogaert, *Anvers.*

CHRONIC PULMONARY HEART DISEASES

P. Broustet, *Bordeaux;* I. Ferrer, *New York;* F. J. Halmagyi, *Glamorgan;* P. Lavenne, *Louvain;* J. MacMichael, *London;* N. G. M. Orie, *Groningen;* J. Turiaf, *Paris;* H. Valentin, *Cologne;* O. L. Wade, *Belfast.*

Tuesday, September 16, 8 P.M.

Reception by the Municipal Magistrates, City Hall of Brussels

Wednesday, September 17, 9 to 11 A.M.

Symposia

AUTOMATION OF THE HEART

O. Gauer, *Bad Nauheim;* A. Guyton, *Jackson;* J. P. Henry, *U.S.A.;* C. Heymans, *Ghent;* B. Folkow, *Göteborg;* M. Mendlowitz, *New York;* U. S. von Euler, *Stockholm.*

PERIPHERAL CIRCULATION

J. Cid dos Santos, *Lisbon;* F. Lund, *Stockholm;* K. Matthes, *Herlangen.*

CORRELATION OF ELECTROCARDIOGRAPHIC AND PATHOLOGIC OBSERVATIONS

R. P. Grant, *Bethesda;* C. E. Kossmann, *New York;* J. Lenègre, *Paris;* R. Scott, *Cleveland;* E. Wolheim, *Wurzberg.*

Wednesday, September 17, 11:15 A.M.

General Conference

Chairman: P. RIJLANT, *Brussels*

Wednesday, September 17, 2 to 4 P.M.

Round Table Discussions

PULMONARY FUNCTION IN MITRAL STENOSIS

D. Caroll, *Baltimore;* J. Dankmeijer, *Leiden;* L. Dexter, *Boston;* G. C. Dogliotti, *Turin;* K. W. Donald, *Birmingham;* H. Landen, *Dusseldorf;* R. Pannier, *Bruges;* L. Werkö, *Gothenburg.*

PERIPHERAL VESSELS

M. de Bakey, *Houston;* F. Kaindl, *Vienna;* J. Lambert, *Spa;* E. Malan, *Genoa;* P. Martin, *Chelmsford;* F. Martorell, *Barcelona;* M. Ratschow, *Darmstadt;* J. van der Stricht, *Brussels;* P. Wertheimer, *Lyon.*

DIAGNOSIS OF CORONARY DISEASES

N. Boyadjian, *Brussels;* E. Cabrera, *Mexico;* L. de Soldati, *Buenos Aires;* H. T. Mankin, *Rochester;* M. Regnier, *Brussels.*

Wednesday, September 17, 8 P.M.

Gala Concert by Belgium's National Orchestra under the direction of André Vandernoot, Main Room of the Palais des Beaux Arts

Thursday, September 18, 9 to 11 A.M.

Symposia

VECTORIAL ELECTROCARDIOGRAPHY

P. Duchosal, *Geneva;* A. Grishman, *New York;* A. Jouve, *Marseilles;* P. Rijlant, *Brussels;* M. Segers, *Brussels,* J. van Heerswynghels, *Brussels.*

COLLAGEN DISEASES

I. Costero, *Mexico;* G. C. Griffith, *Los Angeles;* Löfler, *Zurich;* S. Oram, *London;* E. Rossi, *Zurich.*

SOCIAL CARDIOLOGY

G. Biorck, *Malmö;* Y. Bouvrain, *Paris;* W. Evans, *London;* H. K. Hellerstein, *Cleveland;* Joao Porto, *Coimbra;* J. K. Maddox, *Sydney;* S. Padmavati, *New Delhi;* H. E. Ungerleider, *New York.*

Thursday, September 18, 6 P.M.

Reception in the Congo Pavilion at the International World Exhibition

Thursday, September 18, 8 P.M.

Reception by the Municipal Magistrates, City Hall of Brussels

Friday, September 19, 9 to 11 A.M.

Symposia

CONGENITAL HEART DISEASES

M. Campbell, *London;* J. E. Edwards, *Rochester;* F. Grosse Brockhoff, *Dusseldorf;* P. Soulié, *Paris;* E. Wood, *Rochester.*

CARDIAC INSUFFICIENCY

R. J. Bing, *St. Louis;* Fejfar, *Prague;* F. Lenzi, *Sienna;* J. Lequime, *Brussels;* A. Taquini, *Buenos Aires.*

ARTERIOSCLEROSIS

L. N. Katz, *Chicago;* A. Keys, *Minneapolis;* M. F. Oliver, *Edinburgh;* R. Raynau, *Algiers.*

LOCAL CIRCULATION

S. E. Bradley, *New York;* J. P. Merril, *Boston;* G. Nylin, *Stockholm;* F. Reubi, *Bern.*

Friday, September 19, 11 P.M.

Award of the "Prize of the Belgian Society of Cardiology" and lecture by the Laureate

Friday, September 19, 2 to 4 P.M.

Round Table Discussions

SURGERY OF CONGENITAL HEART DISEASES

O. Bayer, *Berlin;* R. Brock, *London;* A. G. Brom, *Leiden;* C. Craford, *Stockholm;* C. H. Dubost, *Paris;* M. Ellis, *Rochester.*

CARDIAC INSUFFICIENCY

G. Agostoni, *Milan;* J. Brod, *Prague;* P. Cossio, *Buenos Aires;* J. Queralto, *Barcelona;* R. Hegglin, *St. Gallen;* H. Lagerlof, *Stockholm;* J. Moniz de Bettencourt, *Lisbon;* J. V. Warren, *Durham.*

Symposium

GEOGRAPHIC EPIDEMIOLOGY

B. Moia, *Buenos Aires;* N. Kimura, *Fukuoka;* M. Ken awy, *Cairo;* J. Laham, *Damascus;* A. Samia, *Manila;* F. van Dooren, *Brussels;* P. D. White, *Boston.*

Friday, September 19, 8 P.M.

Banquet

Saturday, September 20, 9 to 11 A.M.

Symposium

HEART ADAPTATION

J. P. Bouckaert, *Louvain;* L. Brouha, *Wilmington;* J. Malmejac, *Algiers;* A. Rotta, *Lima;* R. F. Rushmer,

Seattle; S. J. Sarnoff, *Bethesda;* R. Thauer, *Bad Nauheim.*

Round Table Discussion

SUBACUTE BACTERIAL ENDOCARDITIS

M. Finland, *Boston;* G. Hayward, *London;* R. Laplane, *Paris;* E. Magalhaes-Gomès, *Rio de Janeiro;* R. Martin, *Paris;* C. Plavsic, *Belgrade;* Resat Garan, *Istambul;* L. Trias de Bes, *Barcelona.*

HYPERTENSION

P. Bastenie, *Brussels;* E. Braun Menendez, *Buenos Aires;* G. A. Perera, *New York;* W. G. Pickering, *London;* G. Roth, *Rochester.*

Saturday, September 20, 11:15 A.M.

CLOSING SESSION

General Information

The Prize of the Belgian Society of Cardiology: This has aroused a great deal of interest. Thirty-three papers have been submitted to an International board presided over by Sir John Parkinson (London) and composed of I. Chávez (Mexico), L. Condorelli (Rome), D. Routier (Paris), and P. D. White (Boston). The Laureate of this competition will make a verbal statement on his work in the late morning of Friday, September 19.

Technical Exhibit: During the entire Congress, a technical exhibition will be organized on the premises of the Congress. The most recent acquisitions in medical and surgical equipment, pharmaceutical products and cardiological literature will be presented.

Scientific Exhibit: There also will be a scientific exhibition where a great number of documents will show in detail, the research undertakings and the results obtained in the important schools of cardiology.

Film Sessions: Sessions will be organized where the latest films on cardiology will be shown.

Accommodations: Accommodations in Brussels for some 2,500 registrants during the World Exhibition cannot be settled without encountering some difficulties. The Havas Expinter Agency, 15 Blvd. Adolphe Max, is recommended for arrangements. However, other organizations may be utilized at the convenience of those planning to attend the Congress.

Excursions: Tours of the City, the World Exhibition, the charming rural regions as well as other principal attractions of Belgium, will be organized for the registrants and their families.

International Exhibition: All registrants will be given a card allowing free entrance to all the Exhibits, for the duration of the Congress.

Registration: Although the time limit imposed on the registrations has been reached, cardiologists may still forward their registration fee. The Organizing Committee cannot guarantee access to all the planned meetings for those who do not register in advance.

Important Advice: All registrants should report immediately after arrival in Brussels to the Office of the Secretary, 51 avenue Franklin Roosevelt, in order to receive all necessary documents for accommodations, attendance to the Scientific Meetings and the various receptions.

Registration to the Congress: Effective member 1,500 BF; Associate member, 1,000 BF.

Bank Account: Société Générale de Belgique, Montagne-du-Parc 3, Brussels. N° 90.490,

Additional Information is available from the General Secretary, Fr. van Dooren, 80, rue Mercelis, Brussels.

Symposium on Ballistocardiography to be Held in Brussels

The Ballistocardiograph Research Society announces a Symposium to be conducted in conjunction with the Third World Congress of Cardiology in Brussels, September 18, 1958.

Among the outstanding clinical presentations will be a report by Dr. Isaac Starr on the 20-year follow-up of his original normal series.

Further information is available from the Secretary of the Ballistocardiograph Research Society, New Jersey Neuro-Psychiatric Institute, Box 1000, Princeton, New Jersey.

The tentative program of papers to be presented is as follows:

Afternoon Session

Theory of BCG

JOHN NICKERSON: Measurement of Stroke Volume by the Ballistic Method.

H. KLENSCH: Comparison of Cardiac Output Determined by Ultra-Low Frequency Ballistocardiography and Other Methods.

R. CASPARI: Investigations of Cardiac Output during Short Lasting Variations of Environment Temperature by the Ultra-Low Frequency Ballistograph.

W. HOHNEN: Determination of Stroke Volume by an Ultra-Low Frequency Ballistocardiograph. Effect of Nitroglycerin, Adrenalin, Nor-Adrenalin and Cigarette Smoking on Cardiac Output.

ABRAHAM NOORDERGRAAF: The Venous Effect in the Normal Human Ballistocardiogram. Discussion of the Origin of the H-Wave.

SAMUEL TALBOT: Vector Ballistocardiograph.

Evening Session

Clinical

ISAAC STARR: Further 20-Year Studies with the Ballistocardiogram.

LEON DE SOLDATI: Ballistocardiographic Evolution in Angina Pectoris and Its Relationship to the Modification of the Level of Blood Lipids.

ERNST JOKL: Ballistocardiographic Studies on Athletes.

J. MERLEN: The Ballistocardiogram in Myxedema.

WILLIAM SCARBOROUGH and DEWITT HENDEE SMITH: Physiological Correlation of ULF Displacement, Velocity and Acceleration Ballistocardiograms.